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(54) Title: RETROVIRAL PROTEASE INHIBITING COMPOUNDS

(57) Abstract

Inhibitors of HIV protease are provided. When bound to HIV protease, the inhibitors are characterized by a unique three-dimensional conformation and orientation relative to the S1, S1', S2, S2', S3, and S3' subsites of the protease. Pharmaceutical compositions containing the inhibitors and methods of treating HIV infection are also provided.

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RETROVIRAL PROTEASE INHIBITING COMPOUNDS

Cross-Reference to Related Application

The present application is a continuation-in-part of United States Patent Application No. 08/572,226, filed on December 13, 1996 , the disclosure of which is incorporated herein by reference.

Technical Field of the Invention

The present invention relates to novel compounds, compositions and methods for inhibiting retroviral proteases and in particular for inhibiting human immunodeficiency virus (HIV) protease. The present invention also relates to a method of overcoming acquired resistance to certain HIV protease inhibitors.

Background of the Invention

Retroviruses are those viruses which utilize a ribonucleic acid (RNA) intermediate and a RNA-dependent deoxyribonucleic acid (DNA) polymerase, reverse transcriptase, during their life cycle. Retroviruses include, but are not limited to, the RNA viruses of the Retroviridae family, and also the DNA viruses of the Hepadnavirus and Caulimovirus families. Retroviruses cause a variety of disease states in man, animals and plants. Some of the more important retroviruses from a pathological standpoint include human immunodeficiency viruses (HIV-1 and HIV-2), which cause acquired immune deficiency syndrome (AIDS) in man, human T-cell lymphotrophic viruses I, II, IV and V, which cause human acute cell leukemia, and bovine and feline leukemia viruses which cause leukemia in domestic animals.

Proteases are enzymes which cleave proteins at specific peptide bonds. Many biological functions are controlled or mediated by proteases and their

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complementary protease inhibitors. For example, the protease renin cleaves the peptide angiotensinogen to produce the peptide angiotensin I. Angiotensin I is further cleaved by the protease angiotensin converting enzyme (ACE) to form the hypotensive peptide angiotensin II. Inhibitors of renin and ACE are known to reduce high blood pressure in vivo. An inhibitor of a retroviral protease will provide a therapeutic agent for diseases caused by the retrovirus.

The genomes of retroviruses encode a protease that is responsible for the proteolytic processing of one or more polyprotein precursors such as the pol and gag gene products. See Wellink, Arch. Virol. 98 1 (1988). Retroviral proteases most commonly process the gag precursor into core proteins, and also process the pol precursor into reverse transciptase and retroviral protease. In addition, retroviral proteases are sequence specific. See Pearl, Nature 328 482 (1987).

The correct processing of the precursor polyproteins by the retroviral protease is necessary for the assembly of infectious virions. It has been shown that in vitro mutagenesis that produces protease-defective virus leads to the production of immature core forms which lack infectivity. See Crawford, J. Virol. 53 899 (1985); Katoh, et al., Virology 145 280 (1985). Therefore, retroviral protease inhibition provides an attractive target for antiviral therapy. See Mitsuya, Nature 325 775 (1987).

Current treatments for viral diseases usually involve administration of compounds that inhibit viral DNA synthesis. Current treatments for AIDS involve administration of compounds such as 3'-azido-3'-deoxythymidine (AZT), 2',3'-dideoxycytidine (DDC), 2',3'-dideoxyinosine (DDI), d4T and 3TC and compounds which treat the opportunistic infections caused by the immunosuppression resulting from HIV infection. None of the current AIDS treatments have proven to be totally effective in treating and/or reversing the disease. In addition, many of the compounds currently used to treat AIDS cause adverse side effects including low platelet count, renal toxicity and bone marrow cytopenia.

Recently the HIV protease inhibitors ritonavir, saquinavir and indinavir have been approved in the U.S. for treatment of HIV infections. A problem associated with use of existing HIV protease inhibitors is the diminishing effectiveness of those drugs with prolonged use as monotherapy. By way of

example, the long-term administration of ritonavir as monotherapy leads to mutations in the amino acid residue sequence of HIV protease, which mutant HIV proteases have reduced susceptibility to the effects of the inhibitor. Similar results have been reported for other HIV protease inhibitors. There is still a need in the art, therefore, for new and improved HIV protease inhibitors.

Brief Summary of the Invention

The present invention provides HIV protease inhibiting compounds. The inhibitor compounds contain a heterocyclic ring having (a) 4 to 7 ring atoms, (b) at least one ring N atom, and (c) at least one ring C atom which is substituted with oxo (=O), thioxo (=S) or imino (=NH). When bound to the HIV protease, at least one ring atom of that heterocycle is located in either the protease S2 or S2' subsite. The inhibitor preferably binds to the active site of the protease.

The compound of the invention, when bound to the HIV protease, further contains a non-hydrogen atom in either the S1 or S1' subsite of the HIV protease and lacks a non-hydrogen atom in both the S3 and S3' subsites of the HIV protease, which S3 and S3' subsites do not include any of the S1 and S1' subsites, respectively.

The present invention further provides pharmaceutical compositions comprising an HIV protease inhibitor of the invention and the use of inhibitors to inhibit HIV protease or HIV infection alone or in combination with other anti-HIV treatments such as other HIV protease inhibitors or reverse transcriptase inhibitors. The compounds of the present invention are active as inhibitors of mutant HIV proteases, which proteases are resistant to inhibition by ritonavir and other HIV protease inhibitors which promote the development of mutantions in HIV protease of the type promoted by ritonavir. Therefore, the compounds of the present invention are useful in combination with ritonavir and/or other HIV protease inhibitors which promote the development of mutantions in HIV protease of the type promoted by ritonavir.

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Detailed Description of the Invention

I.   The Invention

The present invention provides inhibitors of HIV protease. The inhibitors, when bound to the HIV protease, are characterized by a unique three-dimensional conformation and orientation relative to the HIV protease. As a result of this unique spatial relationship with the HIV protease, the presently claimed inhibitors are less susceptible to the development of mutational changes in the HIV protease of the type caused by monotherapy with ritonavir (or other HIV protease inhibitors which promote the development of mutantions in HIV protease of the type promoted by ritonavir) and which result in loss of inhibitor activity. Further, compounds of the present invention are active as inhibitors of mutant HIV proteases, which proteases are resistant to inhibition by ritonavir and other HIV protease inhibitors which promote the development of mutantions in HIV protease of the type promoted by ritonavir. Thus, an inhibitor of the present invention can be used alone or together with other HIV protease inhibitors to treat HIV infection.

II.   Protease Inhibitor Compounds

A compound of the present invention binds to HIV protease and inhibits the catalytic activity of that protease enzyme. The inhibitor binds to the active site of the HIV protease, which active site is well known in the art (See, e.g., Miller et al., Science, 246:1149-1152, 1989). An inhibitor of the present invention can be either a peptidomimetic or a non-peptide inhibitor as those terms are known and understood in the art (HIV Protease Inhibitors, Kempf, D.J. and Sham, H.L., Current Pharmaceutical Design, 2:225-246, 1996). When bound to the active site, the inhibitor preferably comprises at least one non-hydrogen atom in a first spherical volume. The first spherical volume (and all other spherical volumes referred to herein) is defined by locating the center point of the spherical volume together with a defined radius around that center point. The center points of the spherical volumes are defined by the point of intersection of vectors of a certain length (loci) emanating from particular alpha carbon atoms of the bound protease. One of skill in the art will recognize that any of the alpha carbons of the bound HIV protease can be used as points of reference.

The center point of the first and all other spherical volumes herein is defined by the intersection of at least three vector loci of given lengths (i.e., at least three reference alpha carbons are needed). One of skill in the art will readily appreciate, however, that there can be two spatial coordinates defined by the intersection of three vector loci as defined above. One of the spatial coordinates will be above the plane of the reference alpha carbons and the second will be located below that plane. With particular reference to the present invention (bound inhibitor and protease), one of skill in the art will recognize that one of the two spatial coordinates will be situated deep within the protease itself and, thus, this point in space is not intended to define a spherical volume center point.

The reference points for location of the center point of the first spherical volume herein include the alpha carbon atoms of residues 27, 127, 50 and 150 of the HIV protease. HIV protease consists of two identical subunits, each of which has 99 amino acid residues. As used herein, ordinal numbers 1-99 indicate residues (the N-terminal residue is 1) on one subunit and ordinals 101-199 indicate the corresponding residues on the other subunit. The center point of the first spherical volume is defined by at least three loci selected from the group of first loci consisting of 5.0 Å to 6.0 Å from the alpha carbon of residue 27 of the protease, 5.0 Å to 6.0 Å from the alpha carbon of residue 127 of the protease, 6.3 Å to 7.5 Å from the alpha carbon of residue 50 of the protease, and 6.3 Å to 7.5 Å from the alpha carbon of residue 150 of the protease. Preferably, the center point of the first spherical volume is determined using four loci from the first loci group. The radius of the first spherical volume is about 3.0 Å.

An inhibitor compound of the present invention comprises a particular heterocycle, which heterocycle is uniquely spatially oriented to subsites of the HIV protease, when the inhibitor is bound to the protease. The heterocycle component of the inhibitor can contain from 4 to 7 ring atoms. The ring atoms must include at least one ring nitrogen (N) atom. The ring atoms must also

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include at least one ring carbon (C) atom which is substituted with an oxo (=O) group, a thioxo (=S) group or an imino (=NH) group.

Preferably, the heterocycle of the compound contains five or six ring atoms. The heterocycle preferably contains two non-adjacent ring N atoms and at least one ring C atom which is substituted with an oxo (=O) group. At least one of the ring N atoms preferably has the structure NH and the ring preferably has from 0 to 2 double bonds.

Where the heterocycle has a ring N of the structure NH, the ring N atom of the NH structure is located within a range of from about 2.4 Å to about 3.7 Å of the backbone nitrogen atom of either residue 30 or residue 130 of the protease when the compound is bound to the protease. Where the heterocycle has a ring C atom which is substituted with an oxo (=O) group, the O atom of that C=O group is located within a range of from about 2.4 Å to about 3.7 Å of the backbone nitrogen atom of either residue 30 or residue 130 of the protease when the compound is bound to the HIV protease. Preferably both of the above conditions are satisfied.
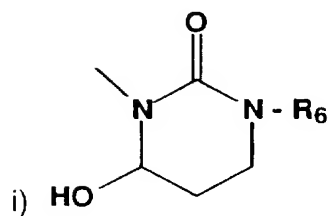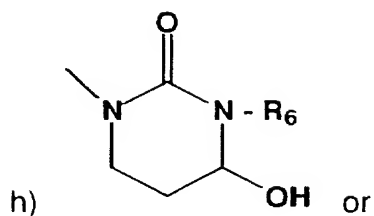
A preferred heterocycle has the structure:
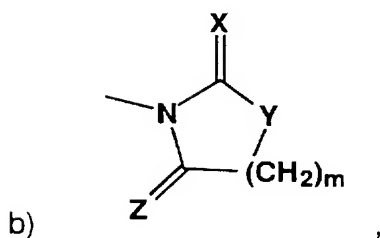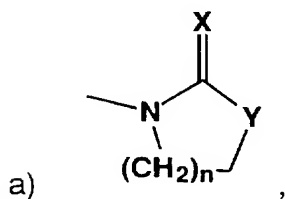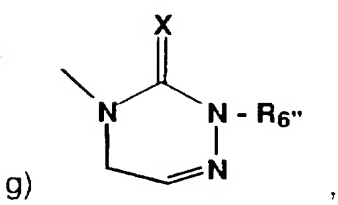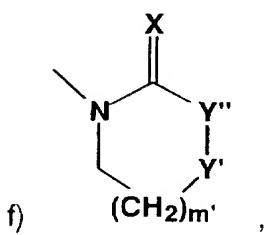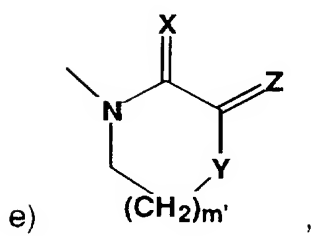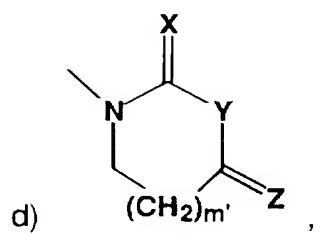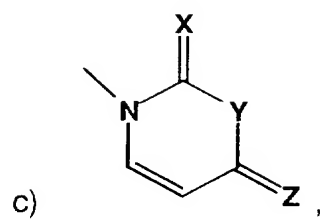
a)

b)

-7-

c)

,

d)

,

e)

,

f)

,

g)

,

-8-

h)

or

i)

wherein n is 1, 2 or 3, m is 1, 2 or 3, m' is 1 or 2, X is O, S or NH, Y is $-CH_2$-, -O-, -S- or $-N(R_6)$- wherein R_6 is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl, Y" is $-CH_2$- or $-N(R_{6''})$- wherein $R_{6''}$ is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl, Y' is $-N(R_{6'})$- wherein $R_{6'}$ is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl, and Z is O, S or NH;

More preferred structures of the heterocycle have the structure:

a)

b)

,

c)

,

d)

    or

e)
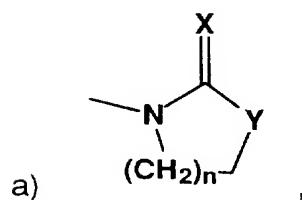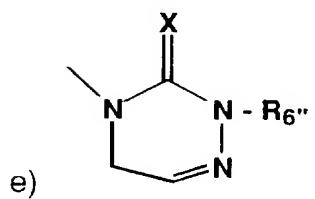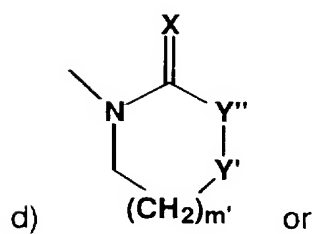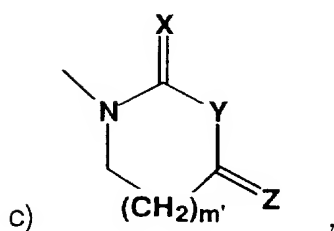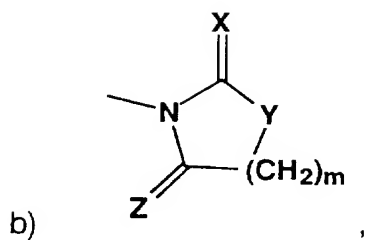
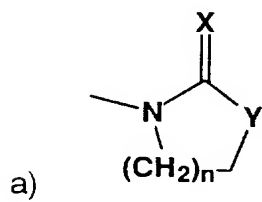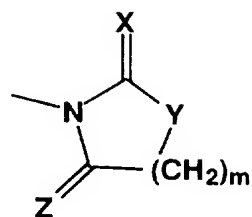wherein X, Y, Y', Y", Z, $R_{6"}$, n, m and m' are defined as above.

More highly preferred heterocycles have the structure:

a)

-10-

wherein n is 1 or 2, X is O or S and Y is -CH$_2$ or -NH-,
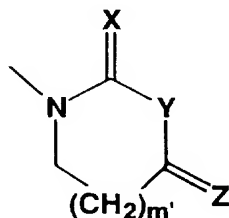
b)

wherein m is 1 or 2, X is O, Y is -CH$_2$- and Z is O,

c)

wherein m' is 1, X is O, Z is O and Y is -NH-,

d)

wherein m' is 1, X is O, Y" is -NH- and Y' is -NH- or

e)
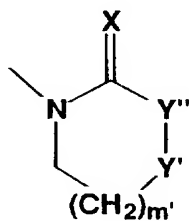
wherein X is O and R$_{6''}$ is hydrogen.

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Even more highly preferred heterocycles have the structure:

a)

wherein n is 1 or 2, X is O or S and Y is -CH$_2$ or -NH-,

b)

wherein m' is 1, X is O, Z is O and Y is -NH-,

c)

wherein m' is 1, X is O, Y" is -NH- and Y' is -NH- or

d)

wherein X is O and R$_{6''}$ is hydrogen.

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Most highly preferred heterocycles have the structure:

wherein n is 1 or 2, X is O or S and Y is -CH$_2$ or -NH-.

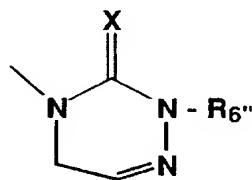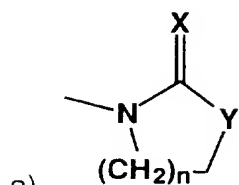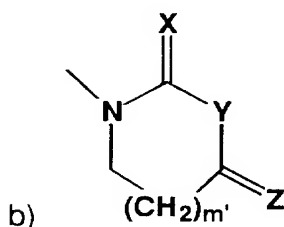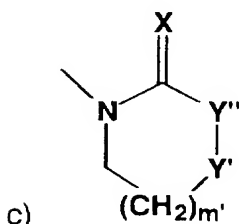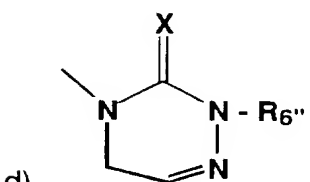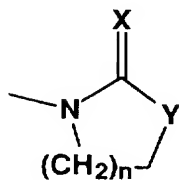When bound to the HIV protease, the inhibitor is characterized by the presence of at least one heterocyclic ring atom in the S2 or S2' subsite of the protease. The locations of the S2 and S2' subsites of the protease are well known to one of skill in the art (See, e.g., Miller et al., *Science*, 246:1149-1152, 1989). Although only one of the heterocyclic ring atoms need be in the defined subsites as defined above, any number of the ring atoms, up to and including the total number of ring atoms (4, 5, 6 or 7), can be located therein. It is preferred that more than one ring atom be located in the S2 or S2' subsite.

More particularly, at least one ring atom of the heterocyclic ring of the inhibitor is located in either a second or third spherical volume. The second spherical volume has a radius in the range of from about 2.5 Å to about 4.0 Å. More preferably, that radius is from about 3.0 Å to about 4.0 Å and, even more preferably in the range of from about 3.5 Å to about 4.0 Å. Most preferably, the radius of the fourth spherical volume is about 4.0 Å. The center point of the second spherical volume is defined by at least three loci selected from a second group of loci consisting of 3.8 Å to 4.2 Å from the alpha carbon of residue 28 of the protease, 4.3 Å to 4.7 Å from the alpha carbon of residue 30 of the protease, 7.7 Å to 8.1 Å from the alpha carbon of residue 32 of the protease, and 6.5 Å to 6.9 Å from the alpha carbon of residue 48 of the protease. The radius of the third spherical volume is in the range of from about 2.5 Å to about 4.0 Å. More preferably, that radius is from about 3.0 Å to about 4.0 Å and, even more preferably in the range of from about 3.5 Å to about 4.0 Å. Most preferably, the radius of the third spherical volume is about 4.0 Å. The center point of the third spherical volume is defined by at least three loci selected from

a group of third loci consisting of 3.8 Å to 4.2 Å from the alpha carbon of residue 128 of the protease, 4.3 Å to 4.7 Å from the alpha carbon of residue 130 of the protease, 7.7 Å to 8.1 Å from the alpha carbon of residue 132 of the protease, and 6.5 Å to 6.9 Å from the alpha carbon of residue 148 of the protease.

The second and third spherical volumes are related by symmetry to the two subunits of the protease. The alpha carbons at residues 28 (128), 30 (130), 32 (132) and 48 (148) are typically Ala, Asp, Val and Gly, respectively. The precise identity of those residues is not, however, critical to their use as reference points for defining the second and third spherical volumes. Thus, each of those residues can be any of the twenty naturally occurring amino acid residues. In other words, mutations in the protease will not affect the location of the defined volumes or the relationship of the inhibitor to that volume.

In a manner similar to that described for the first spherical volume, it is preferred that the center points of the second and third spherical volumes be defined by more than three loci. Thus, these center points are each independently preferably defined by at least four, more preferably at least five, even more preferably at least six and, most preferably all seven of their respective loci groups.

In yet another embodiment, an inhibitor of the present invention is preferably also spatially constrained relative to the S1 and S1' subsites of the protease. In accordance with this embodiment, the inhibitor, when bound to the protease, has at least one non-hydrogen atom in either the S1 or S1' subsite of the protease. More particularly, the inhibitor, when bound to the protease, contains a non-hydrogen atom in either a fourth or a fifth spherical volume. The center point of the fourth spherical volume is defined by the point of intersection of at least three vector loci selected from the group of fourth loci consisting 3.2 Å to 3.7 Å from the alpha carbon of residue 49 of the protease, 4.1 Å to 4.5 Å from the alpha carbon of residue 50 of the protease, 12.4 Å to 12.8 Å from the alpha carbon of residue 108 of the protease, 13.0 Å to 13.4 Å from the alpha carbon of residue 110 of the protease, 11.0 Å to 11.4 Å from the alpha carbon of residue 125 of the protease, 5.7 Å to 6.1 Å from the alpha carbon of residue 182 of the

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protease, and 8.4 Å to 8.8 Å from the alpha carbon of residue 184 of the protease. The radius of the fourth spherical volume is in the range of from about 2.5 Å to about 4.0 Å. More preferably, that radius is from about 3.0 Å to about 4.0 Å and, even more preferably in the range of from about 3.5 Å to about 4.0 Å. Most preferably, the radius of the fourth spherical volume is about 4.0 Å.

The fifth spherical volume (the symmetrical counterpart of the fourth spherical volume but relative to the second subunit of the protease) has a radius in the range of from about 2.5 Å to about 4.0 Å and a center point defined by at least three loci selected from the group of fifth loci consisting of 3.2 Å to 3.7 Å from the alpha carbon of residue 149 of the protease, 4.1 Å to 4.5 Å from the alpha carbon of residue 150 of the protease, 12.4 Å to 12.8 Å from the alpha carbon of residue 8 of the protease, 13.0 Å to 13.4 Å from the alpha carbon of residue 10 of the protease, 11.0 Å to 11.4 Å from the alpha carbon of residue 25 of the protease, 5.7 Å to 6.1 Å from the alpha carbon of residue 82 of the protease, and 8.4 Å to 8.8 Å from the alpha carbon of residue 84 of the protease. A preferred radius for the fifth spherical volume is the same as set forth above for the fourth spherical volume. In preferred embodiments for both the fourth and fifth spherical volumes, the center points are each independently defined by at least four, more preferably at least five, even more preferably at least six and, most preferably seven loci selected from the fourth and fifth loci groups, respectively.

As was the case with the second and third spherical volumes, the precise identity of the amino acid residues at the indicated alpha carbon locations is not critical and they can be any of the twenty naturally occurring amino acid residues.

In still yet another preferred embodiment, an inhibitor of the present invention is spatially constrained relative to the S3 and S3' subsites of the protease. In accordance with this embodiment, the inhibitor, when bound to the protease, lacks a non-hydrogen atom in both the S3 and S3' subsites of the protease. One of ordinary skill in the art will readily appreciate that there is overlap between the S3 and S1 subsites as well as between the S3' and S1'

subsites. The absence of a non-hydrogen atom in the S3 and S3' subsites is intended to exclude those portions of the S3 and S3' subsites overlapping with the S1 and S1' subsites, respectively. In other words, an inhibitor of the present invention can contain a non-hydrogen atom in that portion of S3 overlapping with S1 and that portion of S3' overlapping with S1'.

More particularly, the inhibitor, when bound to the protease, lacks a non-hydrogen atom in both a sixth and seventh spherical volume. The sixth spherical volume has a radius in the range of from about 2.5 Å to about 4.0 Å and a center point defined by at least three loci selected from the group of sixth loci consisting of 7.7 Å to 8.2 Å from the alpha carbon of residue 49 of the protease, 9.8 Å to 10.2 Å from the alpha carbon of residue 50 of the protease, 9.6 Å to 10.0 Å from the alpha carbon of residue 108 of the protease, 10.4 Å to 10.8 Å from the alpha carbon of residue 110 of the protease, 12.7 Å to 13.1 Å from the alpha carbon of residue 125 of the protease, 5.4 Å to 5.8 Å from the alpha carbon of residue 182 of the protease, and 10.1 Å to 10.6 Å from the alpha carbon of residue 184 of the protease. The sixth spherical volume overlaps in part with the fourth spherical volume as defined above. That portion of the sixth spherical volume that overlaps with the fourth spherical volume is excluded from consideration regarding this spatial constraint. In other words, the inhibitor can contain a non-hydrogen atom in that portion of the sixth spherical volume that overlaps with the fourth spherical volume.

The seventh spherical volume has a radius in the range of from about 2.5 Å to about 4.0 Å and a center point defined by at least three loci selected from the group of seventh loci consisting of 7.7 Å to 8.2 Å from the alpha carbon of residue 149 of the protease, 9.8 Å to 10.2 Å from the alpha carbon of residue 150 of the protease, 9.6 Å to 10.0 Å from the alpha carbon of residue 8 of the protease, 10.4 Å to 10.8 Å from the alpha carbon of residue 10 of the protease, 12.7 Å to 13.1 Å from the alpha carbon of residue 25 of the protease, 5.4 Å to 5.8 Å from the alpha carbon of residue 82 of the protease, and 10.1 Å to 10.6 Å from the alpha carbon of residue 84 of the protease, wherein the seventh spherical volume does not include any of the fifth spherical volume. The

exclusion of any of the volume of the fifth spherical volume is in keeping with the overlap between the fifth and seventh spherical volumes.

Preferred values for the radii of the sixth and seventh spherical volumes are the same as set forth above with regard to the fourth and fifth spherical volumes. Similarly, the preferred number of loci used to identify the centerpoints of the sixth and seventh spherical volumes are the same as set forth above relative to the fourth and fifth spherical volumes.

An exemplary and preferred inhibitor compound of the present invention is defined by formula I:

I
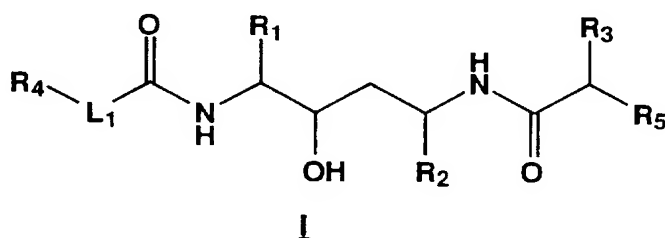
wherein R_1 and R_2 are independently selected from the group consisting of loweralkyl, cycloalkylalkyl and arylalkyl;

R_3 is loweralkyl, hydroxyalkyl or cycloalkylalkyl;

R_4 is aryl or heterocyclic;

R_5 is
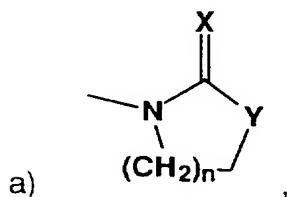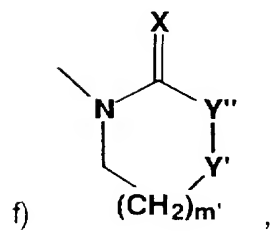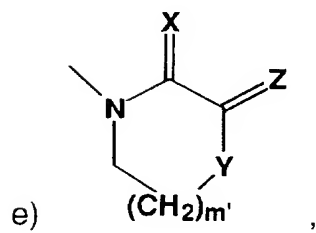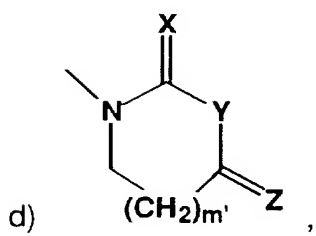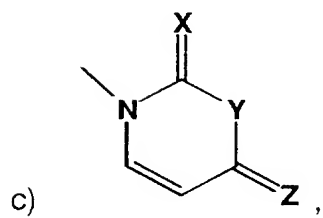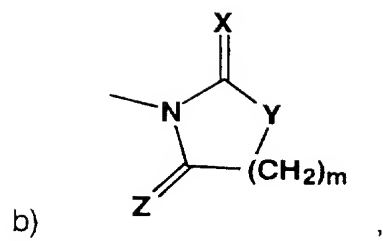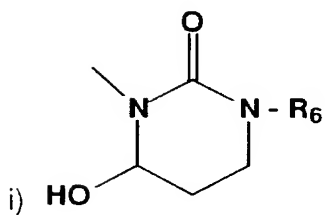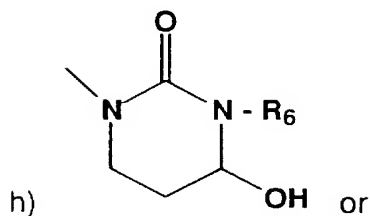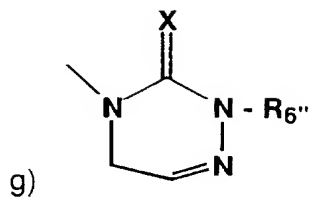
a)   ,

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b)

c)

d)

e)

f)

-18-

g)

,

h)   or

i)

wherein n is 1, 2 or 3, m is 1, 2 or 3, m' is 1 or 2, X is O, S or NH, Y is -CH$_2$-,
-O-, -S- or -N(R$_6$)- wherein R$_6$ is hydrogen, loweralkyl, cycloalkyl,
cycloalkylalkyl, aryl or arylalkyl, Y" is -CH$_2$- or -N(R$_6$")- wherein R$_6$" is hydrogen,
loweralkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl, Y' is -N(R$_6'$)- wherein R$_6'$
is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl, and Z is O,
S or NH;

and

L$_1$ is
a)   -O-,
b)   -S-,
c)   -N(R$_7$)- wherein R$_7$ is hydrogen, loweralkyl, cycloalkyl or cycloalkylalkyl,
d)   -O-alkylenyl-,

e)   -S-alkylenyl-

f)   -S(O)-alkylenyl-,

g) $-S(O)_2$-alkylenyl-,

h) $-N(R_7)$-alkylenyl- wherein R_7 is defined as above,

i)   -alkylenyl-O-,

j)   -alkylenyl-S-,

k)   alkylenyl-$N(R_7)$- wherein R_7 is defined as above,

l)   alkylenyl or

m)   alkenylenyl;

or a pharmaceutically acceptable salt, ester or prodrug thereof.

Preferred compounds are compounds of the formula I wherein R_1 and R_2 are arylalkyl, R_3 is loweralkyl, R_4 is aryl, R_5 is

a)

,

b)

,

c)

,

d)   or

e)
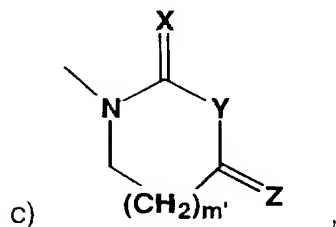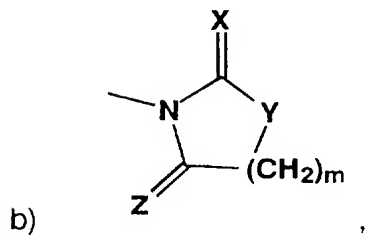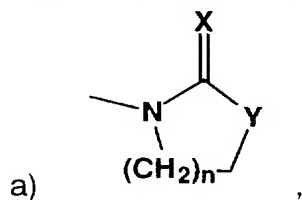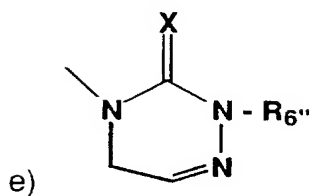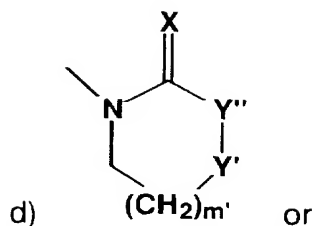
wherein X, Y, Y', Y", Z, $R_{6''}$, n, m and m' are defined as above and
L_1 is -O-alkylenyl.

More preferred compounds are compounds of the formula I wherein R_1
and R_2 are benzyl or R_1 is benzyl and R_2 is loweralkyl, R_3 is loweralkyl, R_4 is
(a) phenyl which is substituted with two loweralkyl groups and which is
optionally substituted with a third substituent selected from the group consisting
of loweralkyl, hydroxy, amino and halo or (b) pyridyl or pyrimidinyl either of
which is substituted with two loweralkyl groups and which is optionally
substituted with a third substituent selected from the group consisting of
loweralkyl, hydroxy, amino and halo, R_5 is
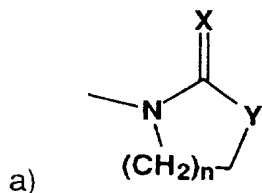
a)

wherein n is 1 or 2, X is O or S and Y is -CH_2 or -NH-,

b)

wherein m is 1 or 2, X is O, Y is -CH$_2$- and Z is O,

c)

wherein m' is 1, X is O, Z is O and Y is -NH-,

d)

wherein m' is 1, X is O, Y" is -NH- and Y' is -NH- or

e)

wherein X is O and R$_6$" is hydrogen

and

L$_1$ is -O-CH$_2$-.

Even more preferred compounds are compounds of the formula I
wherein R$_1$ and R$_2$ are benzyl or R$_1$ is benzyl and R$_2$ is isopropyl, R$_3$ is

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loweralkyl, R$_4$ is 2,6-dimethylphenyl which is optionally substituted with a third substituent selected from the group consisting of loweralkyl and halo, R$_5$ is

a)

wherein n is 1 or 2, X is O or S and Y is -CH$_2$ or -NH-,

b)

wherein m is 1 or 2, X is O, Y is -CH$_2$- and Z is O,

c)

wherein m' is 1, X is O, Z is O and Y is -NH-,

d)
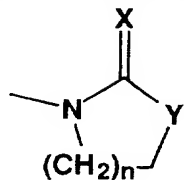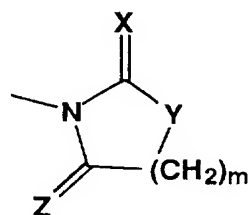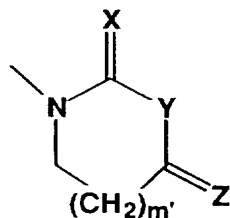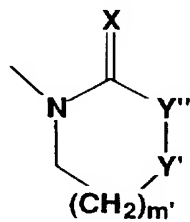
wherein m' is 1, X is O, Y" is -NH- and Y' is -NH- or

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e)
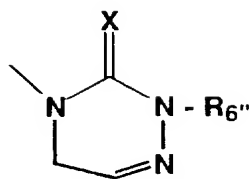
wherein X is O and $R_{6''}$ is hydrogen

and
L_1 is -O-CH_2-.

Most preferred compounds are compounds of the formula I wherein R_1 and R_2 are benzyl or R_1 is benzyl and R_2 is isopropyl, R_3 is loweralkyl, R_4 is 2,6-dimethylphenyl which is optionally substituted with a third substituent selected from the group consisting of loweralkyl and halo, R_5 is

a)

wherein n is 1 or 2, X is O or S and Y is -CH_2 or -NH-,

b)

wherein m' is 1, X is O, Z is O and Y is -NH-,

c)
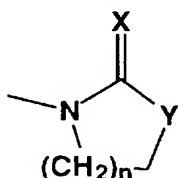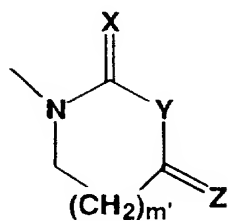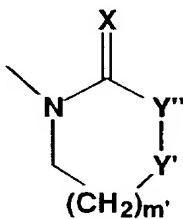
wherein m' is 1, X is O, Y" is -NH- and Y' is -NH- or

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d)
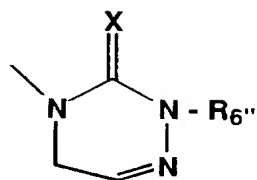
wherein X is O and $R_{6''}$ is hydrogen

and

L_1 is $-O-CH_2-$.

Most highly preferred compounds are compounds of the formula I wherein R_1 and R_2 are benzyl or R_1 is benzyl and R_2 is isopropyl, R_3 is loweralkyl, R_4 is 2,6-dimethylphenyl which is optionally substituted with a third substituent selected from the group consisting of loweralkyl and halo, R_5 is
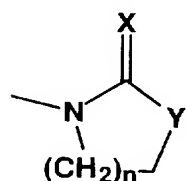
wherein n is 1 or 2, X is O or S and Y is $-CH_2$ or $-NH-$
and

L_1 is $-O-CH_2-$.

Examples of highly and most highly preferred compounds of the formula I are selected from the group consisting of:
(2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane;
(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-(2S-(1-imidazolidin-2-onyl)-3,3-dimethyl butanoyl)amino-1,6-diphenylhexane;
(2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)amino-3-hydroxy-5-(2S-(1-imidazolidin-2-thionyl)-3-methyl butanoyl)amino-1,6-diphenylhexane;

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(2S,3S,5S)-2-(2,4,6-trimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-imidazolidin-2-onyl)-3-methylbutanoyl) amino-1,6-diphenylhexane;
(2S,3S,5S)-2-(4-fluoro-2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-imidazolidin-2-onyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane;
(2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-pyrrolidin-2-onyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane;
(2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-pyrrolidin-2,5-dionyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane;
(2S,3S,5S)-2-(trans-3-(2,6-dimethylphenyl) propenoyl) amino-3-hydroxy-5-(2S-1-tetrahydropyrimidin-2-onyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane;
(2S,3S,5S)-2-(3-(2,6-dimethylphenyl) propanoyl) amino-3-hydroxy-5-(2S-(1-tetrahydropyrimidin-2-onyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane;
(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2,4-dionyl)-3-methylbutanoyl)amino-1,6-diphenylhexane;
(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(4-aza-1-tetrahydro-pyrimid-2-onyl)-3-methyl-butanoyl)amino-1,6-diphenylhexane;
(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl)amino-1-phenyl-6-methylheptane;
(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2,4-dionyl)-3-methylbutanoyl)amino-1-phenyl-6-methylheptane; and
(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(4-aza-4,5-dehydro-1-pyrimid-2-onyl)-3-methyl-butanoyl)amino-1,6-diphenylhexane;
or a pharmaceutically acceptable salt, ester or prodrug thereof.

The most highly preferred compound of the formula I is (2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane;
or a pharmaceutically acceptable salt, ester or prodrug thereof.

In some circumstances it is preferred to be able to prepare (2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane (or a pharmaceutically acceptable salt, ester or prodrug thereof) as an amorphous solid. Such an

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amorphous solid can be prepared by dissolving (2S, 3S, 5S)-2-(2,6-
Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-
3-methyl butanoyl] amino-1,6-diphenylhexane in an organic solvent (for
example, ethanol, isopropanol, acetone, acetonitrile and the like) and then
adding the solution to water. Preferably, (2S, 3S, 5S)-2-(2,6-
Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-
3-methyl butanoyl] amino-1,6-diphenylhexane is dissolved in ethanol (from
about 2 to about 4 mL/g) and the ethanolic solution is added with stirring to
water (from about 10 about 100 mL/g) to provide amorphous (2S, 3S, 5S)-2-
(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-
onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane.

The compounds of the invention can comprise asymmetrically
substituted carbon atoms. As a result, all stereoisomers of the compounds of
the invention are meant to be included in the invention, including racemic
mixtures, mixtures of diastereomers, as well as single diastereomers of the
compounds of the invention.

The terms "S" and "R" configuration are as defined by the IUPAC 1974
Recommendations for Section E, Fundamental Stereochemistry, Pure Appl.
Chem. (1976) 45, 13 - 30.

The term "N-protecting group" or "N-protected" as used herein refers to
those groups intended to protect the N-terminus of an amino acid or peptide or
to protect an amino group against undersirable reactions during synthetic
procedures. Commonly used N-protecting groups are disclosed in Greene and
Wuts, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York
(1991)), which is hereby incorporated by reference. N-protecting groups
comprise acyl groups such as formyl, acetyl, propionyl, pivaloyl,
t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl,
phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl,
4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as
benzenesulfonyl, p-toluenesulfonyl and the like; carbamate forming groups
such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl,
p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl,

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2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl,
3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl,
2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl,
2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl,
1-(p-biphenylyl)-1-methylethoxycarbonyl,
α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl,
t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl,
ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl,
2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl,
fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl,
cyclohexyloxycarbonyl, phenylthiocarbonyl and the like; alkyl groups such as
benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as
trimethylsilyl and the like. Preferred N-protecting groups are formyl, acetyl,
benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc)
and benzyloxycarbonyl (Cbz).

The term "activated ester derivative" as used herein refers to acid halides
such as acid chlorides, and activated esters including, but not limited to, formic
and acetic acid derived anhydrides, anhydrides derived from alkoxycarbonyl
halides such as isobutyloxycarbonylchloride and the like, N-
hydroxysuccinimide derived esters, N-hydroxyphthalimide derived esters, N-
hydroxybenzotriazole derived esters, N-hydroxy-5-norbornene-2,3-
dicarboxamide derived esters, 2,4,5-trichlorophenol derived esters, thiophenol
derived esters, propylphosphonic acid derived anhydrides and the like.

The term "alkanoyl" as used herein refers to $R_{19}C(O)$- wherein R_{19} is a
loweralkyl group.

The term "alkenylenyl" as used herein refers to a divalent group derived
from a straight or branched chain hydrocarbon containing from 2 to 10 carbon
atoms and also containing at least one carbon-carbon double bond. Examples
of alkenylene include -CH=CH-, -CH$_2$CH=CH-, -C(CH$_3$)=CH-,
-CH$_2$CH=CHCH$_2$-, and the like.

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The terms "alkoxy" and "thioalkoxy" as used herein refer to $R_{15}O$- and $R_{15}S$-, respectively, wherein R_{15} is a loweralkyl group.

The term "alkoxyalkoxy" as used herein refers to $R_{22}O$-$R_{23}O$- wherein R_{22} is loweralkyl as defined above and R_{23} is an alkylenyl group. Representative examples of alkoxyalkoxy groups include methoxymethoxy, ethoxymethoxy, t-butoxymethoxy and the like.

The term "alkoxyalkyl" as used herein refers to an alkoxy group appended to a loweralkyl radical.

The term "alkoxycarbonyl" as used herein refers to $R_{20}C(O)$- wherein R_{20} is an alkoxy group.

The term "alkylamino" as used herein refers to -NHR_{16} wherein R_{16} is a loweralkyl group.

The term "alkylaminocarbonyl" as used herein refers to $R_{21}C(O)$- wherein R_{21} is an alkylamino group.

The term "alkylenyl" as used herein refers to a divalent group derived from a straight or branched chain saturated hydrocarbon having from 1 to 10 carbon atoms by the removal of two hydrogen atoms, for example methylene (-CH_2-), 1,2-ethylene (-CH_2CH_2-), 1,1-ethylene =CH-CH_3, 1,3-propylene (-$CH_2CH_2CH_2$-), 2,2-dimethylpropylene (-$CH_2C(CH_3)_2CH_2$-), and the like.

The term "aminocarbonyl" as used herein refers to -$C(O)NH_2$.

The term "aryl" as used herein refers to a mono- or bicyclic carbocyclic ring system comprising 6 to 12 carbon atoms and having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like. Aryl groups can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, halo, haloalkyl, haloalkoxy, alkoxy, alkoxycarbonyl, thioalkoxy, amino, alkylamino, dialkylamino, aminocarbonyl, mercapto, nitro, carboxaldehyde, carboxy and hydroxy.

The term "arylalkyl" as used herein refers to an aryl group as previously defined, appended to a loweralkyl radical, for example, benzyl and the like.

The term "cycloalkyl" as used herein refers to an aliphatic ring system having 3 to 8 carbon atoms including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl, and the like.

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The term "cycloalkylalkyl" as used herein refers to a cycloalkyl group appended to a loweralkyl radical, including but not limited to cyclohexylmethyl.

The term "dialkylamino" as used herein refers to -$NR_{16}R_{17}$ wherein R_{16} and R_{17} are independently selected from loweralkyl groups.

The term "dialkylaminocarbonyl" as used herein refers to $R_{22}C(O)$- wherein R_{22} is a dialkylamino group.

The term "halo" or "halogen" as used herein refers to -Cl, -Br, -I or -F.

The term "haloalkoxy" as used herein refers to $R_{18}O$- wherein R_{18} is a haloalkyl group.

The term "haloalkyl" as used herein refers to a loweralkyl group in which one or more hydrogen atoms are replaced by halogen, for example, chloromethyl, chloroethyl, trifluoromethyl and the like.

The term "heterocyclic ring" or "heterocyclic" or "heterocycle" as used herein refers to any 3- or 4-membered ring containing a heteroatom selected from oxygen, nitrogen and sulfur; or a 5-, 6- or 7-membered ring containing one, two or three heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur or a 5-membered ring containing 4 nitrogen atoms; and includes a 5-, 6- or 7-membered ring containing one, two or three nitrogen atoms; one oxygen atom; one sulfur atom; one nitrogen and one sulfur atom; one nitrogen and one oxygen atom; two oxygen atoms in non-adjacent positions; one oxygen and one sulfur atom in non-adjacent positions; two sulfur atoms in non-adjacent positions; two sulfur atoms in adjacent positions and one nitrogen atom; two adjacent nitrogen atoms and one sulfur atom; two non-adjacent nitrogen atoms and one sulfur atom; two non-adjacent nitrogen atoms and one oxygen atom. The 5-membered ring has 0-2 double bonds and the 6- and 7-membered rings have 0-3 double bonds. The nitrogen heteroatoms can be optionally quaternized. The term "heterocyclic" also includes bicyclic groups in which any of the above heterocyclic rings is fused to a benzene ring or a cyclohexane ring or another heterocyclic ring (for example, indolyl, quinolyl, isoquinolyl, tetrahydroquinolyl, benzofuryl, bistetrahydorfuranyl or benzothienyl and the like). Heterocyclics include: azetidinyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, homopiperidinyl,

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pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, tetrahydrofuranyl, tetrahydrothienyl, thiazolidinyl, isothiazolyl, triazolyl, tetrazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, pyrrolyl, pyrimidyl and benzothienyl. Heterocyclics also include compounds of the formula
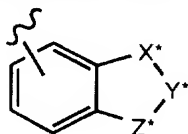
wherein X* is -CH$_2$-, -NH- or -O-, Y* is -C(O)- or [-C(R")$_2$-]$_v$ wherein R" is hydrogen or C$_1$-C$_4$-alkyl and v is 1, 2 or 3 and Z* is -O- or -NH-; such as 1,3-benzodioxolyl, 1,4-benzodioxanyl and the like.

Heterocyclics can be unsubstituted or substituted with one, two, three or four substituents independently selected from the group consisting of hydroxy, halo, oxo (=O), alkylimino (R*N= wherein R* is a loweralkyl group), amino, alkylamino, dialkylamino, alkoxy, alkoxyalkoxy, haloalkyl, cycloalkyl, aryl, arylalkyl, -COOH, -SO$_3$H and loweralkyl. In addition, nitrogen containing heterocycles can be N-protected.

The term "hydroxyalkyl" as used herein refers to a loweralkyl radical to which is appended an hydroxy group.

The term "loweralkyl" as used herein refers to a straight or branched chain alkyl radical containing from 1 to 6 carbon atoms including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl and the like.

The term "thioalkoxyalkyl" as used herein refers to a thioalkoxy group appended to a loweralkyl radical.

The compound of the invention of formula I can be prepared as shown in Schemes I-IV. As outlined in Scheme I, intermediates 1 and 2 (wherein P$_1$ is an N-protecting group, for example, t-butyloxycarbonyl) can be coupled using standard peptide coupling reagents and methods, for example, reaction of 1 and 2 in the presence of 1-hydroxybenzotriazole and a diimide such as

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dicyclohexylcarbodiimide (DCC) or N-ethyl-N'-dimethylaminopropyl carbodiimide (EDAC) and the like to give $\underline{3}$. Alternatively, a salt or an activated ester derivative of intermediate $\underline{1}$ (for example, the acid chloride, prepared by reaction of the carboxylic acid with thionyl chloride) can be reacted with intermediate $\underline{2}$.

Compound $\underline{3}$ can be N-deprotected to give compound $\underline{4}$. N-deprotection of $\underline{3}$ wherein P_1 (especially wherein P_1 is t-butyloxycarbonyl) is an acid labile N-protecting group can lead to formation of impurities resulting from migration of the acyl group R_4-L_1-C(O)- from the amino group to the hydroxyl group. The formation of this impurity can be minimized or eliminated by performing the deprotection using (1) trifluoroacetic acid in methylene chloride or (2) concentrated hydrochloric acid (from about 2 molar equivalents to about 6 molar equivalents, preferably, from about 2 molar equivalents to about 4 molar equivalents) in acetic acid at about room temperature. A preferred N-deprotection method comprises reacting compound $\underline{3}$ (wherein P_1 is t-butyloxycarbonyl) with concentrated hydrochloric acid (from about 10 to about 20 molar equivalents) in acetonitrile (from about 2 to about 10 liters/kilogram of compound $\underline{3}$) at a temperature of from about 0°C to about 5°C. Compound $\underline{5}$ or an activated ester derivative thereof can then be coupled to compound $\underline{4}$ to give the compound of the formula I (i.e., $\underline{6}$).

An alternative process is shown in Scheme IIA. Compound $\underline{7}$ (wherein P_2 is an N-protecting group, for example, benzyloxycarbonyl) can be coupled to compound $\underline{5}$, or a salt or an activated ester derivative thereof (for example, the acid chloride, prepared by reaction of the carboxylic acid with thionyl chloride), to give $\underline{8}$. Compound $\underline{8}$ can be N-deprotected to give $\underline{9}$. Compound $\underline{9}$ can be coupled with compound $\underline{1}$, or an activated ester derivative thereof, to give the compound of the formula I (i.e., $\underline{6}$).

Scheme IIB shows a preferred alternative process wherein the N- protected amino alcohol $\underline{7a}$ (P_3 is hydrogen and P_4 is an N-protecting group or both P_3 and P_4 are N-protecting groups, preferably, P_3 and P_4 are benzyl) is reacted with from about 1 to about 1.3 molar equivalents of carboxylic acid $\underline{5}$ or a salt or an activated ester derivative thereof (for example, the acid chloride, prepared by reaction of the carboxylic acid with thionyl chloride in ethyl acetate or THF or oxalyl chloride in toluene/DMF and the like) in the presence of from

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about 1.0 to about 4.0 molar equivalents (preferably, from about 2.5 to about 3.5 molar equivalents) of an organic amine base (for example, imidazole, 1-methylimidazole, 2-methylimidazole, 2-isopropylimidazole, 4-methylimidazole, 4-nitroimidazole, pyridine, N,N-dimethylaminopyridine, 1,2,4-triazole, pyrrole, 3-methylpyrrole, triethylamine or N-methylmorpholine and the like) or from about 1 to about 20 molar equivalents of an inorganic base (for example, sodium carbonate or sodium bicarbonate and the like) in an inert solvent (for example, ethyl acetate, dimethylformamide, THF, acetonitrile, isopropyl acetate or toluene and the like) at a temperature of from about 0°C to about 50°C to provide compound 8a. Preferred organic amine bases include imidazole and 1,2,4-triazole.

N-Debenzylation of 8a (for example, using hydrogen and a hydrogenation catalyst or Pd/C and a formic acid salt (for example, ammonium formate and the like) or Pd/C and formic acid and the like) provides 9. Compound 9 can be advantageously purified by crystallization with an organic carboxylic acid (for example, S-pyroglutamic acid, succinic acid or fumaric acid and the like). A preferred organic carboxylic acid is S-pyroglutamic acid.

Compound 9 (or an organic carboxylic acid salt of compound 9) is reacted with from about 1.0 to about 1.3 molar equivalents of carboxylic acid 1 or a salt or an activated ester derivative thereof (for example, the acid chloride) in the presence of (1) from about 4 to about 8 molar equivalents (preferably, from about 5 to about 7 molar equivalents) of an inorganic base (for example, $NaHCO_3$, Na_2CO_3, $KHCO_3$, K_2CO_3, NaOH or KOH and the like) in an inert solvent (for example, 1:1 ethyl acetate/water or isopropyl acetate/water or toluene/water or THF/water and the like) at about room temperature or (2) from about 1.0 to about 4.0 molar equivalents (preferably, from about 2.5 to about 3.5 molar equivalents) of an organic amine base (for example, imidazole, 1-methylimidazole, 2-methylimidazole, 2-isopropylimidazole, 4-methylimidazole, 4-nitroimidazole, pyridine, N,N-dimethylaminopyridine, 1,2,4-triazole, pyrrole, 3-methylpyrrole, triethylamine or N-methylmorpholine and the like) in an inert solvent (for example, ethyl acetate, isopropyl acetate, THF, toluene, acetonitrile, dimethylformamide and the like) at a temperature of from about 0°C to about 50°C to provide compound 6.

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In a preferred embodiment of the invention (shown in Scheme III), intermediate compound 5 has the formula of compound 10 (R_3 is as defined for the compound of formula I and is preferably isopropyl). Compound 10 can be prepared in variety ways as shown in Scheme III. In one method, amino acid 11 (either as the free carboxylic acid or as the carboxylic acid ester (i.e., loweralkyl ester)) is converted to carbamate 12 (R" is phenyl, loweralkyl-substituted phenyl, halo-substituted phenyl, nitro-substituted phenyl, trifluoromethylphenyl and the like) by reaction with the appropriate chloroformate ester and the like.

Reaction of carbamate 12 with from about 1.0 to about 1.5 molar equivalents of amine 13 or an acid addition salt thereof (Q is a leaving group, for example, Cl, Br or I, or a sulfonate such as methanesulfonate, triflate, p-toluenesulfonate, benzenesulfonate and the like) in an inert solvent (for example, THF, methyl t-butyl ether, dimethoxyethane, THF/water, dimethoxyethane/water, toluene or heptane and the like) in the presence of a base (for example, LiOH, NaOH, Li_2CO3, Na_2CO_3, lithium phenoxide or sodium phenoxide and the like) in the amount of from about 2.5 to about 3.5 molar equivalents provides urea 14. Urea 14 can be isolated and reacted further or can be converted in situ to cyclic urea 10 by reaction in an inert solvent (for example, THF, dimethoxyethane, methyl t-butyl ether, toluene or heptane and the like) with a base (for example, potassium t-butoxide, sodium hydride, potassium hydride or dimethylaminopyridine and the like) in the amount of from about 2.0 to about 5.0 molar equivalents. If the amino acid ester of 11 was the starting material, the ester is then hydrolyzed to provide the carboxylic acid 10.

Alternatively, amino acid 11 (either as the free carboxylic acid or as the carboxylic acid ester) is converted to urea 14 by reaction with from about 1.0 to about 1.5 molar equivalents of isocyanate 15 (Q is a leaving group, for example, Cl, Br or I, or a sulfonate such as methanesulfonate, triflate, p-toluenesulfonate, benzenesulfonate and the like) in an inert solvent (for example, THF, dimethoxyethane, methyl t-butyl ether, toluene or heptane and the like) in the presence of a base.

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In yet another alternative, amino acid 11 (either as the free carboxylic acid or as the carboxylic acid ester) is converted to diamine 16 by reaction with from about 1.0 to about 1.5 molar equivalents of amine 13 or an N-protected derivative thereof (Q is a leaving group, for example, Cl, Br or I, or a sulfonate such as methanesulfonate, triflate, p-toluenesulfonate, benzenesulfonate and the like) in an inert solvent (for example, THF, dimethoxyethane, methyl t-butyl ether, toluene or heptane and the like) in the presence of a base (for example, NaH or potassium t-butoxide and the like) in the amount of from about 1.0 to about 4.0 molar equivalents. N-deprotection is required if the N-protected derivative of 13 was used. Reaction of diamine 16 with a carbonyl equivalent 17 (for example, phosgene, carbonyldiimidazole and the like wherein Q' and Q" are leaving groups such as Cl, Br, I, -O-loweralkyl, -O-aryl or imidazolyl and the like) in an inert solvent (for example, THF, dimethoxyethane, methyl t-butyl ether, toluene or heptane and the like) in the presence of a base (for example, NaH or potassium t-butoxide and the like and the like) in the amount of from about 2.0 to about 4.0 molar equivalents provides cyclic urea 10. If the amino acid ester of 11 was the starting material, the ester is then hydrolyzed to provide the carboxylic acid 10.

In yet another alternative shown in Scheme IV, compound 11 (either as the free carboxylic acid or as the carboxylic acid ester (i.e., loweralkyl ester)) is reacted with acrylonitrile according to J. Am. Chem. Soc. 72, 2599 (1950) to give aminonitrile 18. Alternatively, acrylonitrile can be replaced with 3-chloropropionitrile to provide 18. N-protection of aminonitrile 18 as the carbamate (R_{30} is loweralkyl or phenyl or haloalkyl (for example, 2-chloroethyl, 2-bromoethyl and the like) and the like) using standard conditions (for example, reaction of the amine with the appropriate chloroformate ester ($ClC(O)OR_{30}$ wherein R_{30} is loweralkyl, phenyl, haloalkyl and the like) neat or in an inert solvent (for example, water, THF and the like) in the presence of an inorganic base (for example, NaOH, KOH, K_2CO_3 and the like) or an organic base (for example, an alkylamine or dialkylamine and the like) and the like) provides compound 19. Hydrogenation of 19 in the presence of a catalyst (for example, Ni-Al alloy (basic) or Raney nickel (neutral or basic) or PtO_2 (acidic) and the like) in an inert solvent (for example, water or methanol or ethanol or THF and

-35-

the like) provides cyclic urea 10. In a preferred process, compound 19 is hydrogenated in the presence of a Ni-Al alloy catalyst in an inert solvent (for example, water or methanol or ethanol or THF and the like) in the presence of a base (for example, KOH or NaOH or LiOH or an organic amine base and the like) in the amount of from about 1.1 to about 5 molar equivalents to provide cyclic urea 10. If the amino acid ester of 11 was the starting material, the ester is then hydrolyzed to provide the carboxylic acid 10.

Alternatively, hydrogenation of compound 18 (as described above for compound 19) provides diamine 16 which can be converted to compound 10 as previously described. If the amino acid ester of 11 was the starting material, the ester is then hydrolyzed to provide the carboxylic acid 10.

Scheme I

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Scheme IIA

Scheme IIB

$P_3=P_4=$benzyl
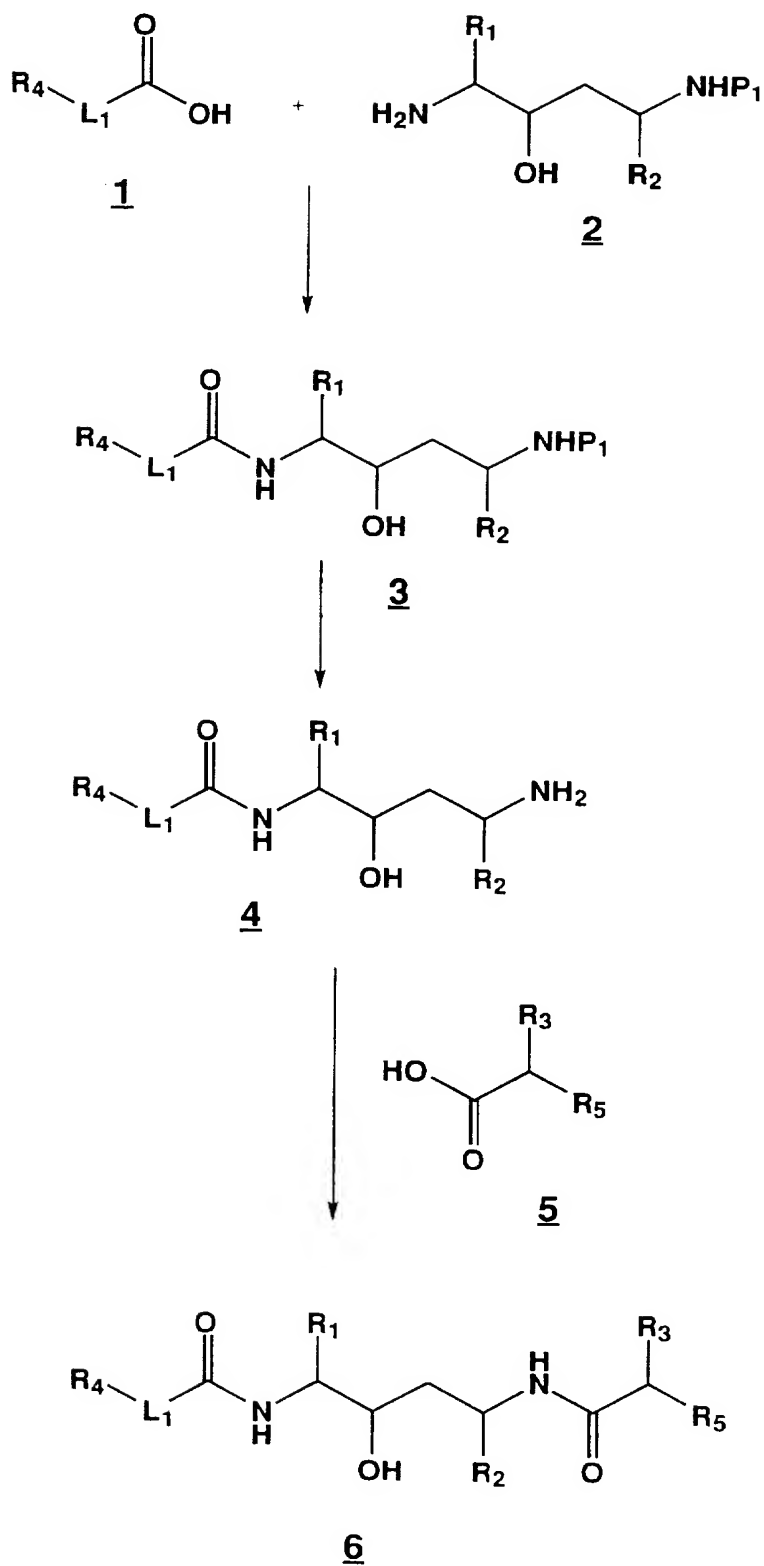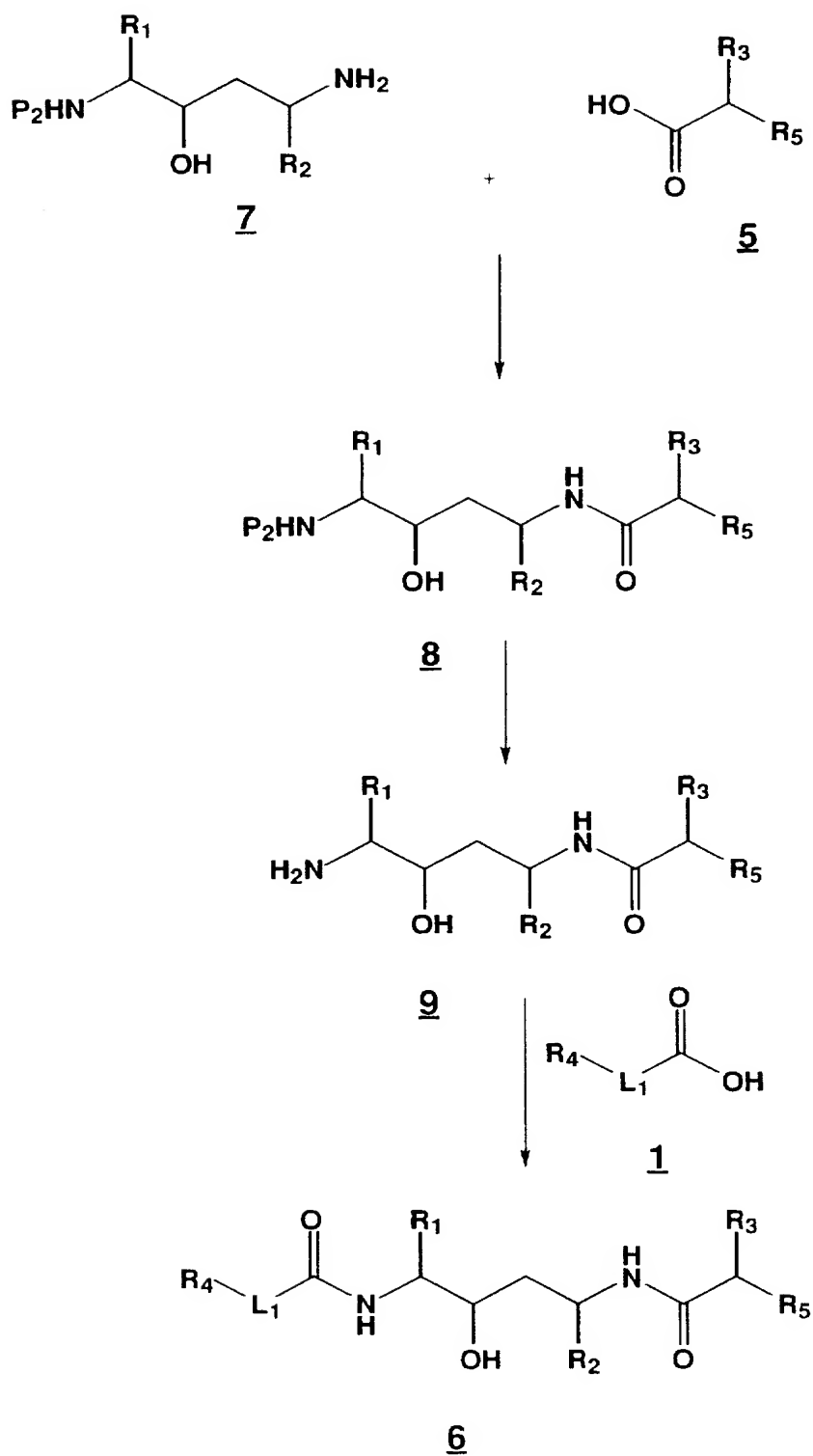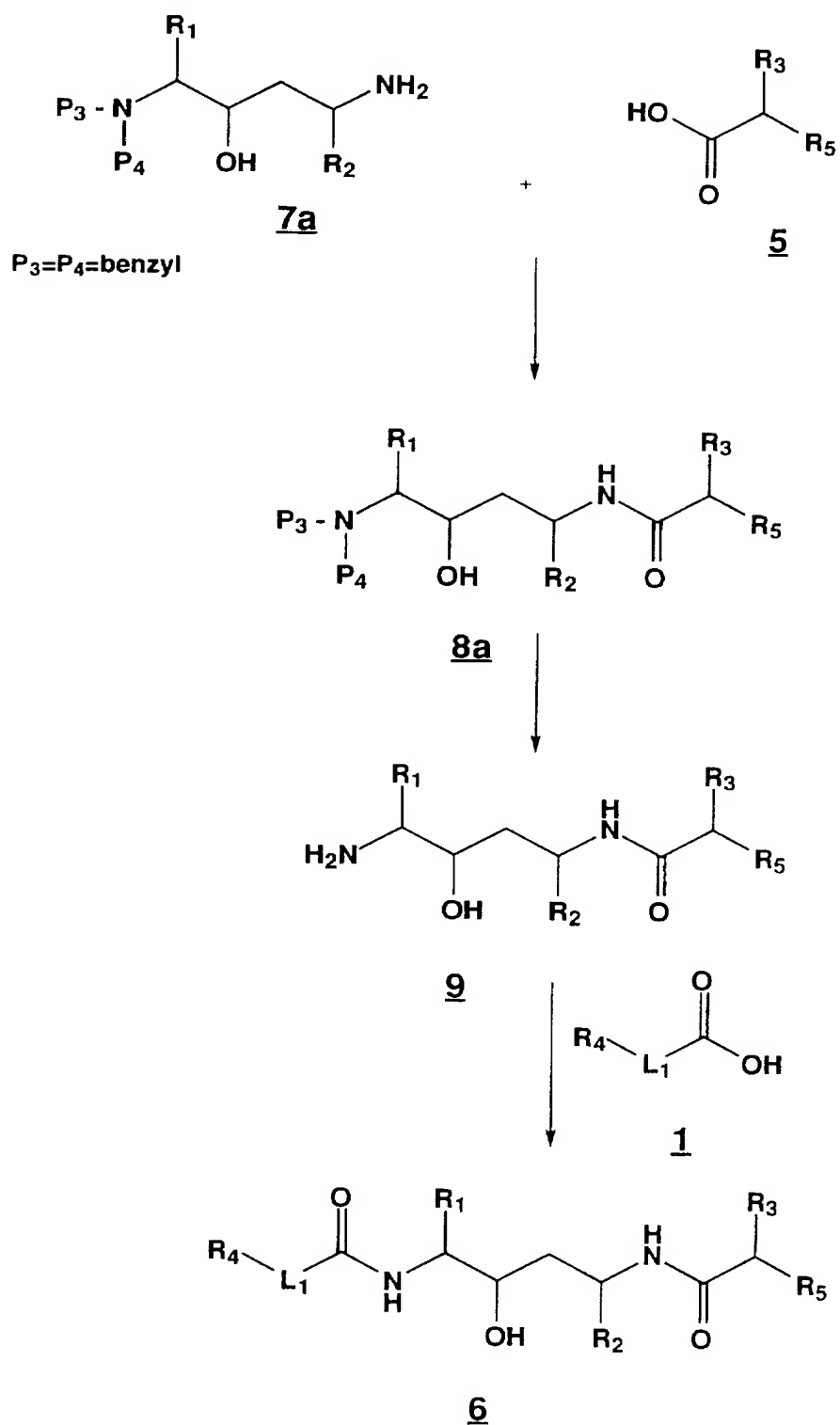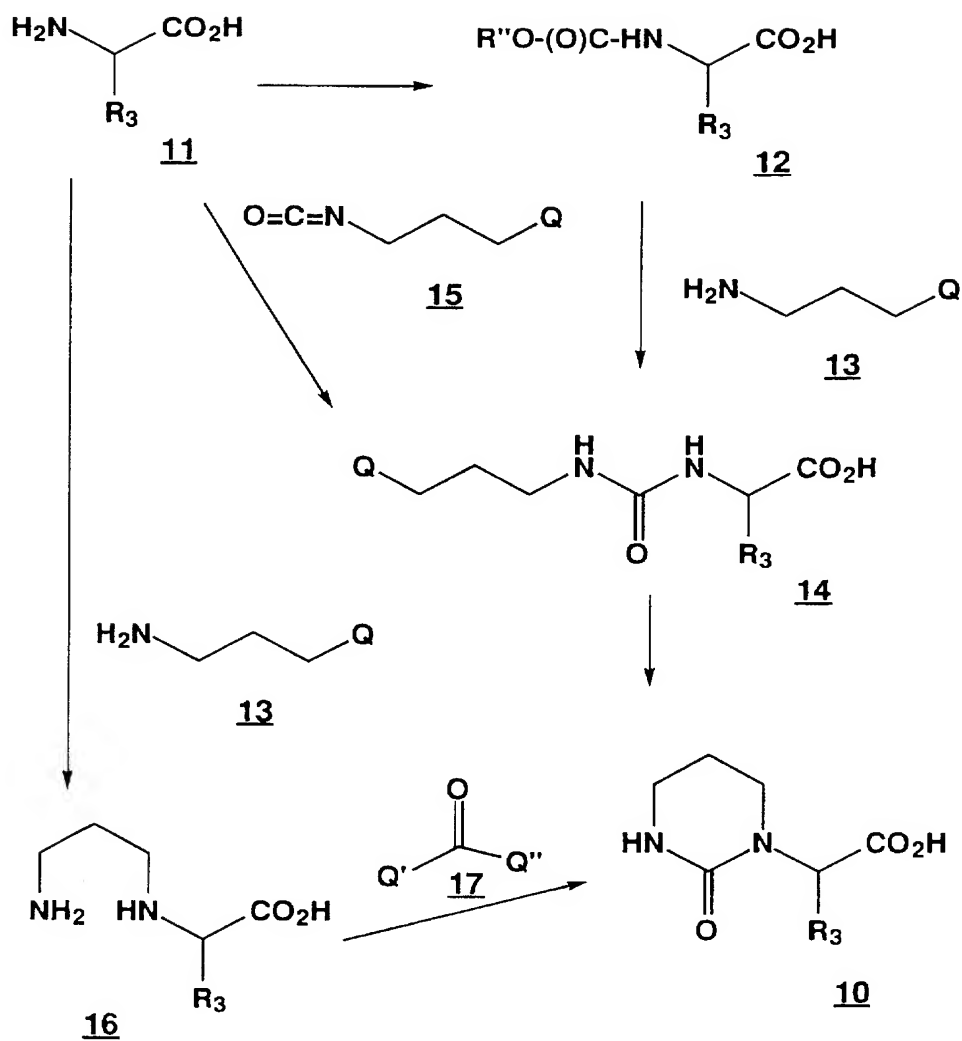
Scheme III

-40-

Scheme IV
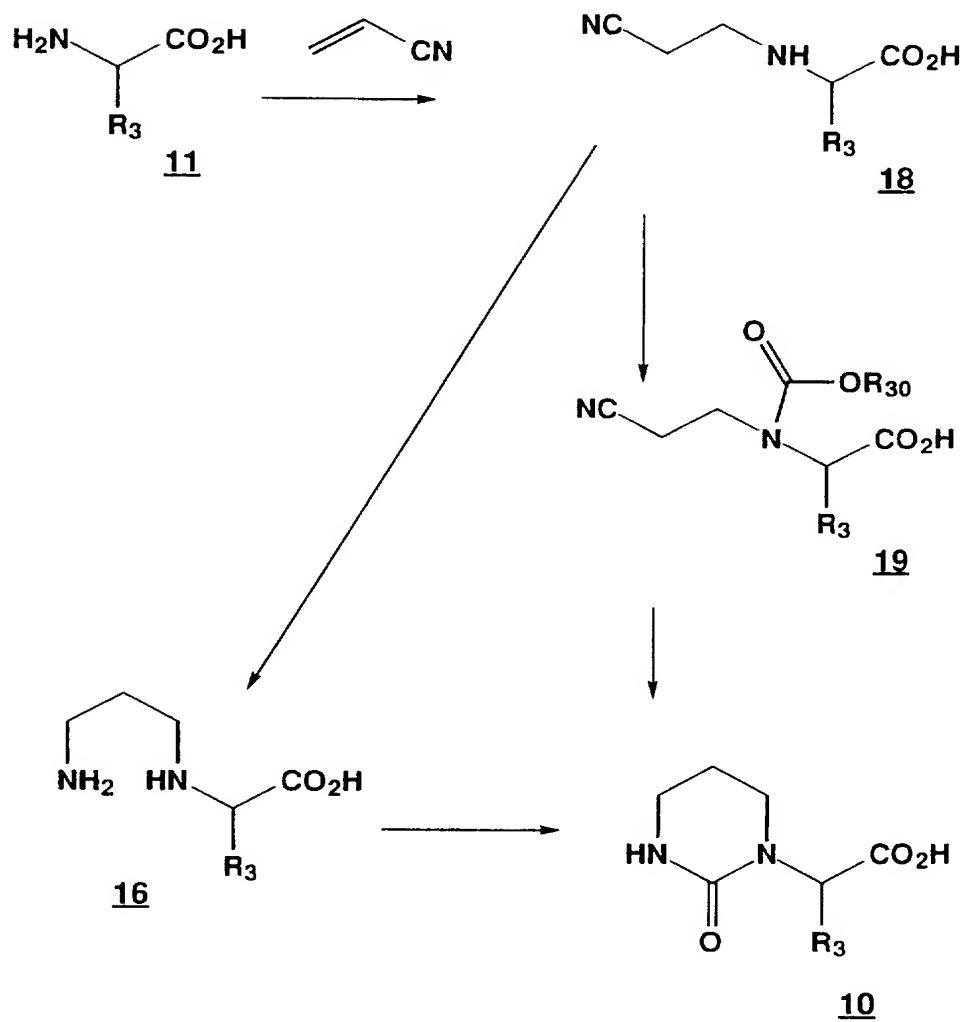
-41-

Key intermediates for the preparation of the compounds of the invention include compounds of the formula **III** or a salt or an activated ester derivative thereof:

III

wherein R_3 is loweralkyl, hydroxyalkyl or cycloalkylalkyl; and

R_5 is

a)

,

b)

,

c)

,

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d)

e)

f)

g)

h)   or

i)

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wherein n is 1, 2 or 3, m is 1, 2 or 3, m' is 1 or 2, X is O, S or NH, Y is -CH$_2$-,
-O-, -S- or -N(R$_6$)- wherein R$_6$ is hydrogen, loweralkyl, cycloalkyl,
cycloalkylalkyl, aryl or arylalkyl, Y" is -CH$_2$- or -N(R$_{6"}$)- wherein R$_{6"}$ is hydrogen,
loweralkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl, Y' is -N(R$_{6'}$)- wherein R$_{6'}$
is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl, and Z is O,
S or NH.

Preferred compounds are compounds of the formula **III** or an activated
ester derivative thereof wherein R$_3$ is loweralkyl and R$_5$ is

a) ,

b) ,

c) ,

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d)   or

e)

wherein X, Y, Y', Y'', Z, $R_{6''}$, n, m and m' are defined as above.

More preferred compounds are compounds of the formula III or an activated ester derivative thereof wherein R_3 is loweralkyl and R_5 is

a)

wherein n is 1 or 2, X is O or S and Y is $-CH_2$ or -NH-,

b)

wherein m is 1 or 2, X is O, Y is $-CH_2-$ and Z is O,

c)

wherein m' is 1, X is O, Z is O and Y is -NH-,

d)

wherein m' is 1, X is O, Y" is -NH- and Y' is -NH- or

e)

wherein X is O and $R_{6''}$ is hydrogen.

Even more preferred compounds are compounds of the formula **III** or an activated ester derivative thereof wherein R_3 is isopropyl and R_5 is

a)

wherein n is 1 or 2, X is O or S and Y is -CH$_2$ or -NH-,

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b)

wherein m is 1 or 2, X is O, Y is -CH$_2$- and Z is O,

c)

wherein m' is 1, X is O, Z is O and Y is -NH-,

d)

wherein m' is 1, X is O, Y" is -NH- and Y' is -NH- or

e)

wherein X is O and R$_{6''}$ is hydrogen.

Most preferred compounds are compounds of the formula III or an activated ester derivative thereof wherein R$_3$ is isopropyl and R$_5$ is
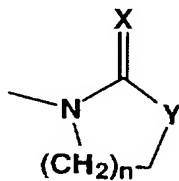
a)

-47-

wherein n is 1 or 2, X is O or S and Y is -CH$_2$ or -NH-,
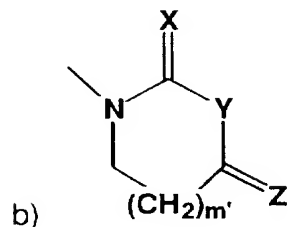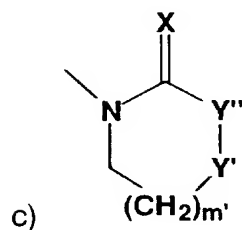
b)

wherein m' is 1, X is O, Z is O and Y is -NH-,

c)

wherein m' is 1, X is O, Y" is -NH- and Y' is -NH- or

d)
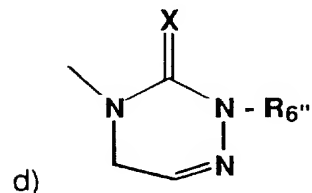
wherein X is O and R$_{6''}$ is hydrogen.

Most highly preferred compounds are compounds of the formula III or an activated ester derivative thereof wherein R$_3$ is isopropyl and R$_5$ is
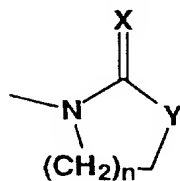
wherein n is 1 or 2, X is O or S and Y is -CH$_2$ or -NH-.

Key intermediates for the preparation of the compounds of the invention
also include compounds of the formula **IV**:

<u>**IV**</u>
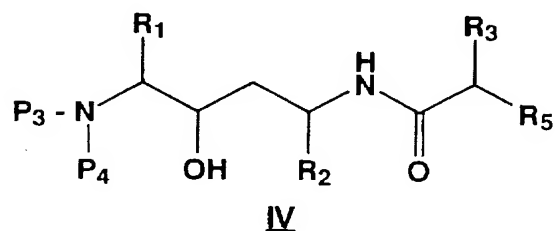
or a salt thereof,

wherein P_3 and P_4 are independently selected from hydrogen or an
N-protecting group;

R_1 and R_2 are independently selected from the group consisting of loweralkyl,
cycloalkylalkyl and arylalkyl;

R_3 is loweralkyl, hydroxyalkyl or cycloalkylalkyl; and

R_5 is

a)   ,

b)   ,

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c)

,

d)

,

e)

,

f)

,

g)

,

h)

or

i)

wherein n is 1, 2 or 3, m is 1, 2 or 3, m' is 1 or 2, X is O, S or NH, Y is -CH$_2$-, -O-, -S- or -N(R$_6$)- wherein R$_6$ is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl, Y" is -CH$_2$- or -N(R$_{6''}$)- wherein R$_{6''}$ is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl, Y' is -N(R$_{6'}$)- wherein R$_{6'}$ is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl, and Z is O, S or NH.

Preferred compounds are compounds of the formula **IV** wherein P$_3$ and P$_4$ are hydrogen or benzyl, R$_1$ and R$_2$ are arylalkyl, R$_3$ is loweralkyl and R$_5$ is
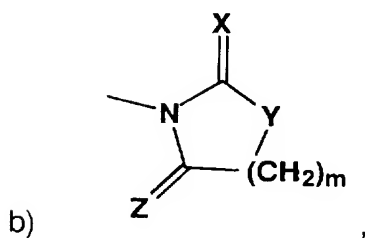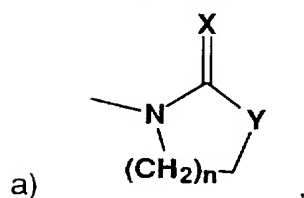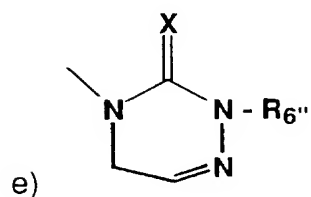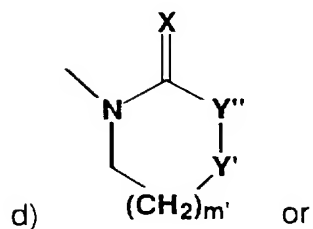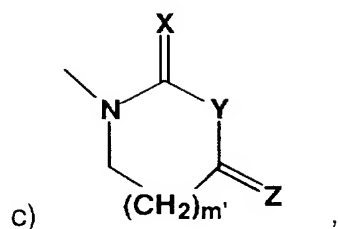
a) ,

b) ,

c)

d)   or

e)

wherein X, Y, Y', Y", Z, $R_{6"}$, n, m and m' are defined as above.

More preferred compounds are compounds of the formula **IV** wherein R_1 and R_2 are benzyl or R_1 is benzyl and R_2 is loweralkyl, R_3 is loweralkyl and R_5 is

a)
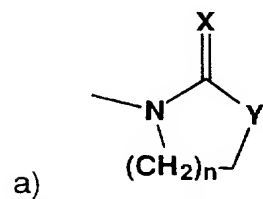
wherein n is 1 or 2, X is O or S and Y is $-CH_2$ or -NH-,

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b)

wherein m is 1 or 2, X is O, Y is -CH$_2$- and Z is O,

c)

wherein m' is 1, X is O, Z is O and Y is -NH-,

d)

wherein m' is 1, X is O, Y" is -NH- and Y' is -NH- or

e)

wherein X is O and R$_{6"}$ is hydrogen.

Even more preferred compounds are compounds of the formula **IV** wherein R$_1$ and R$_2$ are benzyl or R$_1$ is benzyl and R$_2$ is isopropyl, R$_3$ is loweralkyl and R$_5$ is

a)

wherein n is 1 or 2, X is O or S and Y is $-CH_2$ or -NH-,

b)

wherein m is 1 or 2, X is O, Y is $-CH_2-$ and Z is O,

c)

wherein m' is 1, X is O, Z is O and Y is -NH-,

d)

wherein m' is 1, X is O, Y" is -NH- and Y' is -NH- or

e)
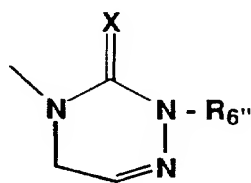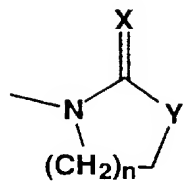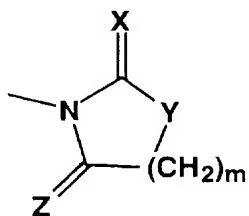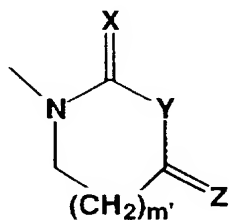
wherein X is O and $R_{6''}$ is hydrogen.

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Most preferred compounds are compounds of the formula **IV** wherein R_1 and R_2 are benzyl or R_1 is benzyl and R_2 is isopropyl, R_3 is loweralkyl and R_5 is

a)

wherein n is 1 or 2, X is O or S and Y is -CH_2 or -NH-,

b)

wherein m' is 1, X is O, Z is O and Y is -NH-,

c)

wherein m' is 1, X is O, Y" is -NH- and Y' is -NH- or

d)
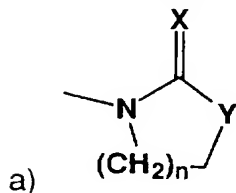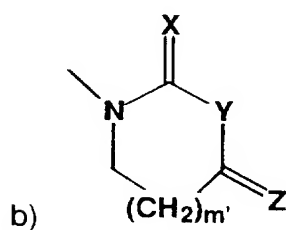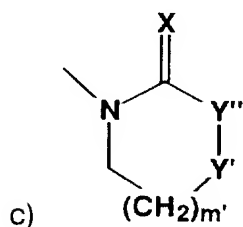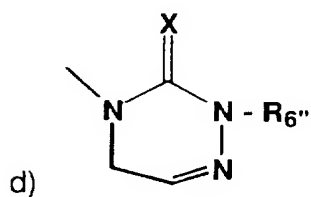
wherein X is O and $R_{6''}$ is hydrogen.

Most highly preferred compounds are compounds of the formula **IV** wherein R_1 and R_2 are benzyl or R_1 is benzyl and R_2 is isopropyl, R_3 is loweralkyl and R_5 is

-55-

wherein n is 1 or 2, X is O or S and Y is -CH$_2$ or -NH-.

Preferred salts of the compound of formula **IV** are organic carboxylic acid salts, especially the (S)-pyroglutamic acid salt.

The following examples will serve to further illustrate the preparation of the novel compounds of the invention.

Example 1
(2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-imidazolidin-2-onyl)-3-methyl-butanoyl] amino-1,6-diphenylhexane.

A. N,N-Dibenzyl-(L)-phenylalanine Benzyl Ester.

A solution containing L-phenylalanine (161 kg, 975 moles), potassium carbonate (445 kg, 3220 moles), water (675 L), ethanol (340 L), and benzyl chloride (415 kg, 3275 moles) was heated to 90±15°C for 10-24 hours. The reaction mixture was cooled to 60°C and the lower aqueous layer was removed. Heptane (850 L) and water (385 L) were added to the organics, stirred, and the layers separated. The organics were then washed once with a water/methanol mixture (150 L/150 L). The organics were then stripped to give the desired product as an oil,which was carried on in the next step without purification.

IR (neat) 3090, 3050, 3030, 1730, 1495, 1450, 1160 cm^{-1}, ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.5-7.0 (m, 20H), 5.3 (d, 1H, J = 13.5 Hz), 5.2 (d, 1H, J = 13.5 Hz), 4.0 (d, 2H, J = 15 Hz), 3.8 (t, 2H, J = 8.4 Hz), 3.6 (d, 2H, J = 15 Hz), 3.2 (dd, 1H, J = 8.4, 14.4 Hz), ^{13}C NMR (300 MHz, CDCl$_3$) δ 172.0, 139.2, 138.0, 135.98.2, 128.1, 128.1, 126.9, 126.2, 66.0, 62.3, 54.3, 35.6.

[α]$_D$ -79° (c = 0.9, DMF).

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B.   (4S)-4-(N,N-Dibenzylamino)-3-oxo-5-phenyl-pentanonitrile.

A solution containing the product of Example 1A (i.e., benzyl ester) (approx. 0.45 moles) in 520 mL tetrahydrofuran and 420 mL acetonitrile was cooled to -40°C under nitrogen. A second solution containing sodium amide (48.7g, 1.25 moles) in 850 mL tetrahydrofuran was cooled to -40°C. To the sodium amide solution was slowly added 75 mL acetonitrile and the resulting solution was stirred at -40°C for more than 15 minutes. The sodium amide/acetonitrile solution was then slowly added to the benzyl ester solution at -40°C. The combined solution was stirred at -40°C for one hour and then quenched with 1150 mL of a 25% (w/v) citric acid solution. The resulting slurry was warmed to ambient temperature and the organics separated. The organics were then washed with 350 mL of a 25% (w/v) sodium chloride solution, then diluted with 900 mL heptane. The organics were then washed three times with 900 mL of a 5% (w/v) sodium chloride solution, two times with 900 mL of a 10% methanolic water solution, one time with 900 mL of a 15% methanolic water solution, and then one time with 900 mL of a 20% methanolic water solution. The organics were stripped and the resulting material dissolved into 700 mL of hot ethanol. Upon cooling to room temperature, the desired product precipitated. Filtration gave the desired product in 59% yield from the L-phenylalanine. IR (CHCl$_3$) 3090, 3050, 3030, 2250, 1735, 1600, 1490, 1450, 1370, 1300, 1215 cm^{-1}, ^{1}H NMR (CDCl$_3$) δ 7.3 (m, 15H), 3.9 (d, 1H, J = 19.5 Hz), 3.8 (d, 2H, J = 13.5 Hz), 3.6 (d, 2H, J = 13.5 Hz), 3.5 (dd, 1H, J = 4.0, 10.5 Hz), 3.2 (dd, 1H, J = 10.5, 13.5 Hz), 3.0 (dd, 1H, J = 4.0, 13.5 Hz), 3.0 (d, 1H, J = 19.5 Hz), ^{13}C NMR (300MHz, CDCl$_3$) δ 197.0, 138.4, 138.0, 129.5, 129.0, 128.8, 128.6, 127.8, 126.4, 68.6, 54.8, 30.0, 28.4. [α]$_D$ -95° (c = 0.5, DMF).

C.   (5S)-2-Amino-5-(N,N-dibenzylamino)-4-oxo-1,6-diphenylhex-2-ene.

To a -5°C solution of the nitrile product of Example 1B (90 Kg, 244 moles) in tetrahydrofuran (288 L), was added benzylmagnesium chloride (378 Kg, 2M in THF, 708 moles). The solution was warmed to ambient temperature and stirred until analysis showed no starting material. The solution was then recooled to 5°C and slowly transferred to a solution of 15% citric acid (465 kg). Additional tetrahydrofuran (85 L) was used to rinse out the original container

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and the rinse was added to the citric acid quench container. The organics were separated and washed with 10% sodium chloride (235 kg) and stripped to a solid. The product was stripped again from ethanol (289 L) and then dissolved in 80°C ethanol (581 L)). After cooling to room temperature and stirring for 12 hours, the resulting product was filtered and dried in a vacuum oven at 30°C to give approx. 95 kg of the desired product.   mp 101-102°C, IR (CDCl$_3$) 3630, 3500, 3110, 3060, 3030, 2230, 1620, 1595, 1520, 1495, 1450 cm^{-1}, ^{1}H NMR (300 MHZ, CDCl$_3$) d 9.8 (br s, 1H), 7.2 (m, 20H), 5.1 (s, 1H), 4.9 (br s, 1H), 3.8 (d, 2H, J = 14.7 Hz), 3.6 (d, 2H, J = 14.7Hz), 3.5 (m, 3H), 3.2 (dd, 1H, J = 7.5, 14.4 Hz), 3.0 (dd, 1H, J = 6.6, 14.4 Hz), ^{13}C NMR (CDCl$_3$) d 198.0, 162.8, 140.2, 140.1, 136.0, 129.5, 129.3, 128.9, 128.7, 128.1, 128.0, 127.3, 126.7, 125.6, 96.9, 66.5, 54.3, 42.3, 32.4.   [α]$_D$ -147° (c = 0.5, DMF).

D.   (2S, 3S, 5S)-5-Amino-2-(N,N-dibenzylamino)-3-hydroxy-1,6-diphenyl-hexane

i) A suspension of sodium borohydride (6.6 kg, 175 moles) in tetrahydrofuran (157 L) was cooled to less than -10±5°C. Methanesulfonic acid (41.6 kg, 433 moles) was slowly added and the temperature kept below 0°C during the addition. Once the addition was complete, a solution of water (6 L, 333 moles), the product of Example 1C (20 kg, 43 moles) and tetrahydrofuran (61 L) was slowly added while maintaining the temperature below 0°C during the addition. The mixture was stirred for not less than 19h at 0±5°C.

ii) To a separate flask was added sodium borohydride (6.6 kg, 175 moles) and tetrahydrofuran (157 L). After cooling to -5±5°C, trifluoroacetic acid (24.8 kg, 218 moles) was added while maintaining the temperature below 15°C. The solution was stirred 30 min at 15±5°C and was then added to the reaction mixture resulting from step i, keeping the temperature at less than 20°C. This was stirred at 20±5°C until reaction was complete. The solution was then cooled to 10±5°C and quenched with 3N NaOH (195 kg). After agitating with *tert*-butyl methyl ether (162 L), the organic layer was separated and washed one time with 0.5N NaOH (200 kg), one time with 20% w/v aqueous ammonium chloride (195 kg), and two times with 25% aqueous

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sodium chloride (160 kg). The organics were stripped to give the desired product as an oil which was used directly in the next step.

IR (CHCl$_3$) 3510, 3400, 3110, 3060, 3030, 1630, ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.2 (m, 20H), 4.1 (d, 2H, J = 13.5 Hz), 3.65 (m, 1H), 3.5 (d, 2H, J = 13.5 Hz), 3.1 (m, 2H), 2.8 (m, 1H), 2.65 (m, 3H), 1.55 (m, 1H), 1.30 (m, 1H), ^{13}C NMR (300 MHz, CDCl$_3$) δ 140.8, 140.1, 138.2, 129.4, 129.4, 128.6, 128.4, 128.3, 128.2, 126.8, 126.3, 125.7, 72.0, 63.6, 54.9, 53.3, 46.2, 40.1, 30.2.

E. (2S,3S,5S)-2-(N,N-Dibenzylamino)-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane.

To a solution of the [2S,3S,5S]-2-N,N-dibenzylamino-3-hydroxy-5-amino-1,6-diphenylhexane (approx. 105 kg, 226 moles) in MTBE (1096 L), was added BOC Anhydride (65 kg, 373 moles) and 10% potassium carbonate (550 kg). This mixture was stirred until reaction was complete (approx. 1 hour). The bottom layer was removed and the organics were washed with water (665 L). The solution was then stripped to give the desired product as an oil. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.40 (s,9H), 1.58 (s, 2H), 2.45-2.85 (m, 4H), 3.05 (m, 1H), 3.38 (d, 2H), 3.6 (m, 1H), 3.79 (m, 1H), 3.87 (d, 2H), 4.35 (s, 1H), 4.85 (s, broad, 1H), 7.0-7.38 (m, 20 H).

F-1. (2S,3S,5S)-2-Amino-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane.

To a stirred solution of [2S,3S,5S]-2-N,N-dibenzylamino-3-hydroxy-5-t-butyloxycarbonylamino-1,6-diphenylhexane (12 g, 21.3 mmol) in methanol (350 mL) was charged ammonium formate (8.05 g, 128 mmol, 6.0 eq) and 10% palladium on carbon (2.4 g). The solution was stirred under nitrogen at 60 °C for three hours and then at 75 °C for 12 hours. An additional amount of ammonium formate (6 g) and 10% palladium on carbon (1.5 g) was added as well as 1 mL of glacial acetic acid. The reaction was driven to completion within 2 hours at a reflux temperature. The reaction mixture was then cooled to room temperature and then filtered through a bed of celite. The filter cake was washed with methanol (75 mL) and the combined filtrates were concentrated under reduced pressure. The residue was taken up in 1 N NaOH (300 mL) and extracted into methylene chloride (2 X 200 mL). The combined organic layers

were washed with brine (250 mL) and dried over sodium sulfate. Concentration of the solution under reduced pressure provided the desired product as a light colored oil which slowly crystallized upon standing (5 g). Further purification of the product could be accomplished by flash chromatography (silica gel, 5% methanol in methylene chloride). 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.42 (s, 9H), 1.58 (m, 1H), 1.70 (m, 1H), 2.20 (s, broad, 2H), 2.52 (m, 1H), 2.76-2.95 (m, 4H), 3.50 (m, 1H), 3.95 (m, 1H), 4.80 (d, broad, 1H), 7.15-7.30 (m, 10H).

F-2. [2S,3S,5S]-2-Amino-3-hydroxy-5-t-butyloxycarbonylamino-1,6-diphenylhexane succinate salt

To a solution of [2S,3S,5S]-2-N,N-dibenzylamino-3-hydroxy-5-t-butyloxycarbonylamino-1,6-diphenylhexane(approx. 127 kg, 225 moles) in methanol (437 L), was added a methanolic (285 L) slurry of 5% palladium on carbon (24 kg). To this was added a solution of ammonium formate (84 kg, 1332 moles) in methanol (361 L). The solution was heated to 75°C for 6-12 hours and then cooled to room temperature. Solids were filtered from the reaction mixture using a filter coated with filteraid (Celite) and the methanol was stripped from the reaction mixture using heat and vacuum (up to 70°C). The residue was dissolved in isopropyl acetate (4400 kg) with heat (40°C) and then washed with a 10% sodium carbonate solution (725 kg), and finally with water (665 L). Both of the washes were performed at 40°C to keep the product in solution. The solvent was removed under vacuum with heat (up to 70°C). Isopropyl alcohol (475 L) was then added and stripped off to remove residual solvents. Isopropanol (1200 L) was added to the residue and stirred until homogeneous. To this solution was added a solution of succinic acid (15-40 kg) in isopropanol (1200 L). The solution jacket was heated to 70°C to dissolve all of the solids and then allowed to slowly cool to room temperature and stir for 6 hours. The solution was then filtered to give the desired product as a white solid (55-80 kg).

mp: 145-146 °C. ^{1}H NMR: (Me$_2$SO-d$_6$, 300 MHz) δ 0.97 (d, 3H, IPA), 1.20 (s, 9H), 1.57 (t, 2H), 2.20 (s, 2H, succinic acid), 2.55 (m, 2H), 2.66 (m, 2H), 2.98 (m, 1H), 3.42 (m, 1H), 3.70 (m, 1H), 3.72 (m, 1H, IPA), 6.60 (d, 1H, amide NH), 7.0-7.3 (m, 10H).

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^{1}H NMR: (CD$_3$OD, 300 MHz) δ 1.11 (d, 3H, J=7 Hz, IPA), 1.29 (s, 9H), 1.70 (m, 2H), 2.47 (s, 2H, succinic acid), 2.65 (m, 2H), 2.85 (m, 2H), 3.22 (m,1H), 3.64 (m, 1H), 3.84 (m, 1H), 7.05-7.35 (m, 10H).

G. Ethyl 2,6-dimethylphenoxy acetate.

To a solution of 2,6-dimethylphenol (8.0 g, 66 mmole) in dioxane (600 ml) was added ethyl bromoacetate (18.2 ml, 164 mmole) and cesium carbonate (58 g, 176 mmole). The reaction mixture was heated at reflux for 18 h, cooled to room temperature, filtered and concentrated in vacuo. Purification by silica gel column chromatography (5% to 20% ether in hexane) provided the desired compound (80%). 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.35 (t, J = 7.5 Hz, 3H), 2.30 (s, 6H), 4.31 (q, J = 7.5 Hz, 2H), 4.40 (s, 2H), 7.0 (m, 3H).

H. 2,6-Dimethylphenoxy acetic acid.

To a solution of the compound from Example 1G (5.15 g, 24.7 mmole) in methanol (170 ml) and water (56 ml) was added 5.3 g of lithium hydroxide at 0°C, the solution was stirred for 1.5 h at RT and concentrated in vacuo. The residue was acidified with 0.5M HCl and extracted with ethyl acetate (300 ml). The organic layer was dried and concentrated to give a white solid (4.05 g, 91%). 300 MHz ^{1}H NMR (CDCl$_3$) δ 2.30 (s, 6H), 4.48 (s, 2H), 7.0 (m, 3H).

I. (2S, 3S, 5S) -2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane.

Coupling of the amine from Example 1F with the acid from Example 1H using standard EDAC coupling procedure provided the desired compound (78%). 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.40 (s, 9H), 1.65 (m, 3H), 2.18 (s, 6H), 2.78 (m, 2H), 2.98 (d, J = 9 Hz, 2H), 3.75 (m, 1H), 3.90 (m, 1H), 4.15 (m, 1H), 4.20 (s, 2H), 4.60 (m, 1H), 7.0 (m, 3H), 7.25 (m, 10H). Mass spectrum: (M = H)$^+$ = 547.

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J. 2-N-(Benzyloxycarbonyl) amino-acetaldehyde.

To a solution of 1.45 ml of DMSO in 20 ml of CH_2Cl_2 at -78°C was added dropwise 1.34 ml of oxalyl chloride. After 15 minutes at -78°C, a solution of

N-Cbz-aminoethanol in 40 ml of CH_2Cl_2 was added. After 15 minutes at -78°C and 2 minutes at 0°C, the solution was cooled to -78°C and triethylamine (6.14 ml) was added dropwise. The solution was stirred at -78°C for 30 minutes and poured into 50 ml of cold 10% aq. citric acid and extracted with ether (150 ml). The combined organic layer was washed with brine and dried with anhydrous Na_2SO_4; filtered and concentrated in vacuo. Purification of the crude product by silica gel column chromatography (10% EtOAc/CH_2Cl_2) provided the desired compound (42%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 4.17 (d, J = 6 Hz, 2H), 5.15 (s, 2H), 5.40 (br s, 1H), 7.36 (m, 5H), 9.66 (s, 1H). Mass spectrum: $(M+NH_4)^+ = 211$.

K. N-(Benzyloxycarbonylamino)-ethyl valine methyl ester.

To a solution of the aldehyde from Example 1J (0.829 g, 4.29 mmole) in 17 ml of methanol was added valine methyl ester hydrochloride (0.72 g, 4.29 mmole), sodium acetate (0.7 g, 8.58 mmole), and sodium cyanoborohydride (0.54 g, 8.58 mmole. The mixture was stirred at RT overnight and the solvent was evaporated in vacuo. The residue was taken up in ethyl acetate (100 ml) and washed with satd. $NaHCO_3$ (10 ml) and the aq. layer was extracted with ethyl acetate (2 x 50 ml). The combined organic layer was washed with brine and dried with anhy. sodium sulfate, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (20% EtOAc/CH_2Cl_2) to provide the desired compound (60%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J = 3 Hz, 3H), 0.94 (d, J = 3 Hz, 3H), 1.90 (m, 1H), 2.55 (m, 1H), 2.80 (m, 1H), 2.98 (d, J = 6 Hz, 1H), 3.20 (m, 1H), 3.30 (m, 1H), 3.71 (s, 3H), 5.10 (s, 2H), 5.27 (br s, 1H), 7;.37 (m, 5H). Mass spectrum: $(M+H)^+ = 309$.

L. 2S-(1-Imidazolidin-2-onyl)-3-methyl butanoic acid methyl ester.

The Cbz-protecting of the compound in Example 1K was removed by hydrogenolysis and the crude product was treated with one equivalent of 1,1,-

carbonyldiimidazole in CH_2Cl_2 to provide the desired compound (64%), 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.95 (d, J = 7.5 Hz, 3H), 0.98 (d, J = 7.5 Hz, 3H), 2.15 (m, 1H), 3.47 (m, 3H), 3.71 (s, 3H), 3.73 (m, 1H), 4.23 (d, J = 10.5 Hz, 1H), 4.81 (br s, 1H), Mass spectrum: $(M+H)^+$ = 201.

M. 2S-(1-Imidazolidin-2-onyl)-3-methyl butanoic acid.

To a solution of the compound from Example 1L (151 mg, 0.75 mmole) in 2.5 ml of water and 5 ml of dioxane was added at 0°C lithium hydroxide monohydrate (2.0 eq.). The solution was stirred at 0°C for 1.5 h and RT for 1 h. Acidification with 1N HCl, extraction with EtOAc (100 ml + 2 x 50 ml), dried with sodium sulfate and evaporation of the filtered solution in vacuo provided the desired compound (88%). 300 MHz ^{1}H NMR (DMSO-d_6) δ 0.85 (d, J = 12 Hz, 3H), 0.92 (d, J = 12 Hz, 3H), 2.05 (m, 1H), 3.25 (m, 2H), 3.30 (m, 1H), 3.50 (m, 1H), 3.90 (d, J = 15 Hz, 1H), 6.40 (br s, 1H), 12.60 (br s, 1H). Mass spectrum: $(M+H)^+$ = 187.

N. (2S, 3S, 5S) -2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-amino-1,6-diphenylhexane.

To 4.5 g of the compound from Example 1I was added 40 ml each of CH_2Cl_2 and trifluoroacetic acid. The solution was left at RT for 1 h. Concentration of the solution in vacuo provided the desired compound (100%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.48 (m, 1H), 1.62 (m, 1H), 2.05 (m, 1H), 2.24 (s, 6H), 2.50 (m, 1H), 2.80 (m, 1H), 3.0-3.10 (m, 4H), 3.90 (d, J = 10 Hz, 1H), 4.17 (m, 1H), 4.26 (ABq, J = 13.5 Hz, 2H), 7.0 (m, 3H), 7.10 (m, 2H), 7.30 (m, 7H), 7.41 (d, J = 10 Hz, 1H). Mass spectrum: $(M+H)^+$ = 447.

O. (2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-imidazolidin-2-onyl)-3-methyl-butanoyl] amino-1,6-diphenylhexane.

Coupling of the amino compound from Example 1N with the acid from Example 1M using standard coupling procedure [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide in DMF] provided the desired compound. (80%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.83 (d, J = 6 Hz, 3H), 0.86 (d, J = 6 Hz, 3H), 1.75 (m, 2H), 2.16 (m, 1H), 2.18 (s, 6H), 2.76 (m, 2H), 2.97 (d, J = 7.5 Hz, 2H), 3.14 (m, 2H),

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3.30 (m, 2H), 3.70 (d, J = 1- Hz, 1H), 3.75 (m, 1H), 4.20 (m, 4H), 4.50 (br s, 1H), 6.70 (d, J = 7.5 Hz, 1H), 7.0 (m, 3H), 7.25 (m, 10H). Mass Spectrum: $(M+H)^+$ = 615.

Example 2
(2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane.

A. 2S-(1-Tetrahydro-pyrimid-2-onyl)-3-methyl butanoic acid.

Using the procedures described in Examples 1J to 1M, but replacing the N-Cbz-aminoethanol in Example 1J with N-Cbz-3-aminopropanol provided the desired compound. 300 MHz ^{1}H NMR (DMSO-d$_6$) δ 0.82 (d, J = 7 Hz, 3H), 0.93 (d, J - 7 Hz, 3H), 1.77 (m, 2H), 2.10 (m, 1H), 3.10-3.23 (m, 4H), 4.42 (d, J = 10.5 Hz, 1H), 6.37 (br s, 1H). Mass spectrum: $(M+H)^+$ = 201.

B. (2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane.

Coupling of the amino compound from Example 1N with the acid from Example 2A using standard procedure (EDAC in DMF) provided the desired compound (70%). 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.80 (d, J = 4.5 Hz, 3H), 0.83 (d, J = 4.5 Hz, 3H), 1.50 (m, 1H), 1.65-1.72 (m, 6H), 2.20 (s, 6H), 2.68 (m, 1H), 2.82 (m, 2H), 3.0 (d, J =7.5 Hz, 1H), 3.05 (m, 4H), 3.77 (m, 1H), 4.07 (d, J = 4.5 Hz, 1H), 4.20 (m, 4H), 4.50 (br s, 1H), 6.78 (br d, 1H), 7.0 (m, 3H), 7.25 (m, 10H). Mass spectrum: $(M+H)^+$ = 629.

Example 3
(2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(3-oxazolidin-2-onyl)-3-methyl-butanoyl] amino-1,6-diphenylhexane.

A. 2S-(3-Oxazolidin-2-onyl)-3-methyl-butanoic acid methyl ester.

To a solution of L-valine methyl ester hydrochloride (7.6 mmole) was added a solution of ethylene oxide in ethanol (1.5 equivalent). The solution was kept at 0°C for 0.5 h and then at RT for 18 h, at which time 0.01 equivalent

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of $BF_3 \cdot Et_2O$ was added. Fresh ethylene oxide was bubbled directly into the solution for 3 to 4 minutes. After 8 h the solution was concentrated to dryness and the residue was dissolved in CH_2Cl_2 and cooled to 0°C. To this solution was added 1.2 equivalents of triethylamine and 1.0 equivalent of triphosgene. After 1 h, the solvent was removed in vacuo and the residue was washed with water (30 ml) and extracted with CH_2Cl_2 (3x50 ml), dried and concentrated. Purification of the crude product by silica gel column chromatography (5% $EtOAc/CH_2Cl_2$) provided the desired compound (42%, 2 steps). 300 MHz ^1H NMR ($CDCl_3$) δ 0.98 (d, J = 4.0 Hz, 3H), 1.0 (d, J = 4.0 Hz, 3H), 2.16 (m, 1H), 3.60 (m, 2H), 3.73 (s, 3H), 4.20 (d, J = 10 Hz, 1H), 4.37 (m, 2H). Mass spectrum: $(M+H)^+$ = 202.

B. 2S-(3-Oxazolidin-2-onyl)-3-methyl-butanoic acid.

Hydrolysis of the methyl ester from Example 3A, using the procedure described in Example 1M provided the desired compound. 300 MHz ^1H NMR ($DMSO-d_6$) δ 0.90 (d, J = 6 Hz, 3H), 0.95 (d, J = 6 Hz, 3H), 2.1 (m, 1H), 3.55 (m, 1H), 3.70 (m, 1H), 3.88 (d, J = 9 Hz, 1H), 4.30 (m, 2H), 13.0 (br s, 1H). Mass spectrum: $(M+NH_4)^+$ = 205.

C. (2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(3-oxazolidin-2-onyl)-3-methyl-butanoyl] amino-1,6-diphenylhexane.

Coupling of the amine from Example 1N with the acid from Example 3B using standard coupling procedures (EDAC in DMF) provided the desired compound. 300 MHz ^1H NMR ($CDCl_3$) δ 0.83 (d, J = 4.5 Hz, 3H), 0.87 (d, J = 4.5 Hz, 3H), 1.75 (m, 1H), 2.10 (m, 1H), 2.20 (s, 6H), 2.65 (m, 1H), 2.85 (m, 1H), 3.0 (m, 3H), 3.30 (m, 1H), 3.60 (m, 2H), 3.77 (m, 1H), 4.20 (m, 4H), 6.25 (br d, J = 6 Hz, 1H), 7.0 (m, 3H), 7.25 (m, 10H). Mass spectrum: $(M+H)^+$ = 616.

Example 4
(2S,3S,5S)-2-[(3R, 3aS, 6aR)-Bis-tetrahydrofuranyloxy] amino-3-hydroxy-5-[2S-(3-methyl-1-imidazolidin-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane.

A. 2S-(3-Methyl-1-imidazolidin-2-onyl)-3-methyl butanoic acid methyl ester.

To a suspension of 45 mg (60% oil dispersion) of sodium hydride in 0.5 ml of DMF was added a solution of 150 mg of the compound from Example 1L in 4.5 ml of DMF. After 20 minutes at RT, (1.5 equivalent, 0.07 ml) methyl iodide was added. Reaction was complete in 1 h. The reaction was quenched with satd. NH_4Cl solution and extracted with ether (100 ml + 50 ml x 2), dried and concentrated in vacuo. The crude product was purified by silica gel column chromatography (20% EtOAc/CH_2Cl_2) to provide the desired compound (61%). 300 MHz ^1H NMR ($CDCl_3$) δ 0.95 (d, J = 6 Hz, 3H), 0.97 (d, J = 6 Hz, 3H, 2.15 (m, 1H), 2.80 (s, 3H), 3.32 (m, 3H), 3.60 (m, 1H), 3.70 (s, 3H), 4.25 (d, J = 10.5 Hz, 1H). Mass spectrum: $(M+H)^+$ = 215.

B. 2S-(3-Methyl-1-imidazolidin-2-onyl)-3-methyl butanoic acid.

Hydrolysis of the methyl ester from Example 4A using the procedure described in Example 1M provided the desired compound. 300 MHz ^1H NMR (DMSO-d_6) δ 0.85 (d, J = 6 Hz, 3H), 0.92 (d, J = 6 Hz, 3H), 2.05 (m, 1H), 2.65 (s, 3H), 3.25 (m, 3H), 3.42 (m, 1H), 3.90 (d, J = 10 Hz, 1H). Mass spectrum: $(M+H)^+$ = 201.

C. (3R,3aS,6aR)-Bis-tetrahydrofuranyl-(4-nitrophenyl) carbonate.

To a solution of 3R-hydroxy-(3aS,6aR)-bis-tetrahydrofuran [J. Med. Chem. **37**, 2506-2508 (1994)] (200 mg, 1.54 mmole) in 10 ml of CH_2Cl_2 was added triethylamine (0.26 ml, 1.85 mmole), and p-nitrophenyl chloroformate (341 mg, 1.69 mmole). The solution was kept at RT for 3 days, diluted with CH_2Cl_2 (100 ml) and washed with satd. $NaHCO_3$ (15 ml). The organic layer was dried and concentrated in vacuo. Purification by silica gel column chromatography (5% EtOAc/CH_2Cl_2) provided the desired compound (42%). 300 MHz ^1H NMR ($CDCl_3$) δ 2.0 (m, 1H), 2.20 (m, 1H), 3.18 (m, 1H), 4.0 (m, 3H), 4.17 (m, 1H), 5.27 (m, 1H), 5.80 (d, J = 6 Hz), 7.40 (d, J = 7.5 Hz, 2H), 8.30 (d, J = 7.5 Hz, 2H). Mass spectrum: $(M+NH_4)^+$ = 313.

D.   (2S,3S,5S)-2-[(3R,3aS,6aR)-Bis-tetrahydrofuranyloxy] amino-3-hydroxy-5-(t-butyloxy carbonyl) amino-1,6-diphenylhexane.

To a solution of the carbonate from Example 4C (100 mg, 0.34 mmole) in 3.4 ml of DMF was added the compound from Example 1F (130 mg, 0.34 mmole). The solution was kept at RT overnight and then concentrated in vacuo. Purification of the crude product by silica gel column chromatography (2% to 5% MeOH/CH$_2$Cl$_2$) provided the desired compound (93%). 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.40 (s, 9H), 1.64 (m, 3H), 2.76 (m, 2H), 2.87 (m, 2H), 3.66-4.0 (m, 7H), 4.53 (m, 1H), 5.06 (m, 2H), 5.68 (d, J = 6 HZ, 1H), 7.10-7.28 (m, 10H). Mass spectrum: (M+NH$_4$)$^+$ = 558.

E.   (2S,3S,5S)-2-[(3R,3aS,6aR)-Bis-tetrahydrofuranyloxy] amino-3-hydroxy-5-amino-1,6-diphenylhexane.

To a solution of the compound from Example 4D (170 mg, 0.31 mmole) in 5 ml of CH$_2$Cl$_2$ was added 5 ml of trifluoroacetic acid. After 0.25 h, the solvent was removed in vacuo. The residue was dissolved in 100 ml of EtOAc and washed with satd. NaHCO$_3$ and then brine, dried and concentrated to provide the desired compound (91%). 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.27-1.60 (m, 4H), 1.75 (m, 2H), 2.47 (m, 1H), 2.80 (m, 1H), 2.88 (m, 2H), 3.0 (m, 2H),3.80 (m, 4H), 4.0 (m, 1H), 5.10 (m, 1H), 5.30 (d, J = 10.5 Hz, 1H), 5.70 (d, J = 6 Hz, 1H), 7.05-7.25 (m, 10H). Mass spectrum: (M+H)$^+$ = 441.

F. (2S,3S,5S)-2-[(3R, 3aS, 6aR)-Bis-tetrahydrofuranyloxy] amino-3-hydroxy-5-[2S-(3-methyl-1-imidazolidin-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane.

Coupling of the carboxylic acid from Example 4B with the amino compound from Example 4E using standard procedure (EDAC in DMF) provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.82 (d, J = 3H, 3H), 0.85 (d, J = Hz, 3H), 1.65 (m, 1H), 2.77 (s, 3H), 2.85 (m, 3H), 3.17 (m, 2H) 3.47 (m, 1H), 3.60 (m, 2H), 3.75 (m, 1H), 3.87 (m, 1H), 4.0 (m, 1H), 4.20 (m, 1H), 5.05 (m, 2H), 5.68 (d, J = 6 Hz, 1H), 6.45 (br d, J = 7.5 Hz, 1H), 7.20 (m, 10H). Mass spectrum: (M+H)$^+$ = 623.

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Example 5

(2S,3S,5S)-2-[(3R,3aS,6aR)-Bis-tetrahydrofuranyloxy] amino-3-hydroxy-5-[2S-(1-imidazolidin-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane.

Coupling of the amino compound from Example 4E with the carboxylic acid from Example 1M using standard procedure (EDAC/DMF) provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.85 (d, J = 7 Hz, 3H), 0.88 (d, J = Hz, 3H), 1.70 (m, 2H, 2.18 (m, 1H), 2.80 (m, 3H), 2.95 (m, 1H), 3.20 (m, 4H), 3.60 (m, 3H), 3.75 (m, 2H), 4.0 (m, 1H), 4.20 (m, 1H), 4.45 (s, 1H), 5.10 (m, 2H), 5.67 (d, J = 6 Hz, 1H) 6.60 (d, J = 7.5 Hz, 1H), 7.20 (m, 10H). Mass spectrum: (M+H)$^+$ = 609.

Example 6

(2S,3S,5S)-2-(N-((5-Thiazolyl)methoxycarbonyl)amino)-5-((2S-(1-imidazolidin-2-onyl)-3-methyl-butanoyl)-amino)-3-hydroxy-1,6-diphenylhexane.

A. Ethyl 2-Chloro-2-formylacetate.

To a three neck 2L round bottom flask charged with potassium t-butoxide (0.5 mol, 500 mL of a 1 M solution in THF) and 500 mL of dry THF cooled to 0°C was added dropwise from an addition funnel a solution of ethyl chloroacetate (0.5 mol, 53.5 mL) and ethyl formate (0.5 mol, 40.4 mL), in 200 mL of THF over 3 hours. After completion of addition, the reaction mixture was stirred for 1 hour and allowed to stand overnight. The resulting solid was diluted with diethyl ether and cooled in an ice bath. Then, the pH was lowered to approximately 3 using 6N HCl. The organic phase was separated, and the aqueous layer was washed 3 times with diethyl ether. The combined ethereal portions were dried over NaSO$_4$, and concentrated in vacuo. The crude desired compound was stored at -30°C and used without further purification.

B. Ethyl Thiazole-5-carboxylate.

To a round bottom flask was added 250 mL of dry acetone, 7.5 g (0.123 mol) of thioformamide, and 18.54 g (0.123 mol) of ethyl 2-chloro-2-formylacetate. The reaction was heated at reflux for 2 hours. The solvent was

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removed in vacuo, and the residue was purified by chromatography (SiO₂, 6 cm o.d. column, 100% CHCl₃, R_f = 0.25) to provide 11.6 g (60%) of the desired compound as a light yellow oil. NMR (CDCl₃ δ 1.39 (t, J = 7 Hz, 3H), 4.38 (q, J = 7 Hz, 2H), 8.50 (s, 1H), 8.95 (s, 1H).

C. 5-(Hydroxymethyl)thiazole.

To a precooled (ice bath) three neck 500 mL flask containing lithium aluminum hydride (2.89 g, 76 mmol) in 250 mL of THF was added ethyl thiazole-5-carboxylate (11.82 g, 75.68 mmol) in 100 mL of THF dropwise over 1.5 hours to avoid excess foaming. The reaction was stirred for an additional hour, and treated cautiously with 2.9 mL of water, 2.9 mL of 15% NaOH, and 8.7 mL of water. The solid salts were filtered, and the filtrate set aside. The crude salts were heated at reflux in 100 mL of ethyl acetate for 30 minutes. The resulting mixture was filtered, and the two filtrates were combined, dried over Na₂SO₄, and concentrated in vacuo. The product was purified by silica gel chromatography eluting sequentially with 0% - 2% - 4% methanol in chloroform, to provide the desired compound, Rf - 0.3 (4% methanol in chloroform), which solidified upon standing in 75% yield. NMR (CDCl₃) δ 4.92 (s, 2H), 7.78 (s, 1H), 8.77 (s, 1H). Mass spectrum: (M+H)⁺ = 116.

D. ((5-Thiazolyl)methyl)-(4-nitrophenyl)carbonate.

A solution of 3.11 g (27 mmol) of 5-(hydroxymethyl)thiazole and excess N-methyl morpholine in 100 ml of methylene chloride was cooled to 0°C and treated with 8.2 g (41 mmol) of 4-nitrophenyl chloroformate. After being stirred for 1 h, the reaction mixture was diluted with CHCl₃, washed successively with 1N HCl, saturated aqueous NaHCO₃, and saturated brine, dried over NaSO₄, and concentrated in vacuo. The residue was purified by silica gel chromatography (SiO₂, 1-2% MeOH/CHCl₃, Rf = 0.5 in 4% MeOH/CHCl₃) to yield 5.9 g (78%) of the desired compound as a yellow solid. NMR (CDCl₃) δ 5.53 (s, 2H), 7.39 (dt, J = 9, 3 Hz, 2H), 8.01 (s, 1H), 8.29 (dt, J = 9, 3 Hz, 2H), 8.90 (s, 1H). Mass spectrum: (M+H)⁺ = 281.

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E. (2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-3-hydroxy-1,6-diphenylhexane.

Coupling of the amino compound from Example 1F with the carbonate from Example 6D using the procedure from Example 4D, followed by removal of the Boc-protecting group using TFA/CH$_2$Cl$_2$ provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.3-1.6 (m, 2H), 2.40 (dd, J = 14, 8 Hz, 1H), 2.78 (dd, J = 5 Hz, 1H), 2.88 (d, J = 7 Hz, 2H), 3.01 (m, 1H), 3.72 (br q, 1H), 3.81 (br d, J = 10 Hz, 1H), 5.28 (s, 2H), 5.34 (br d, J = 9 Hz, 1H), 7.07 (br d, J = 7 Hz, 2H), 7.15-7.35 (m, 8H), 7.87 (s, 1H), 8.80 (s, 1H). Mass spectrum: (M+H)$^+$ = 426.

F. (2S,3S,5S)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-5-((2S-(1-imidazolidin-2-onyl)-3-methyl-butanoyl)-amino)-3-hydroxy-1,6-diphenylhexane.

Coupling of the amino compound from Example 6E with the carboxylic acid from Example 1M using standard procedure (EDAC in DMF) provided the desired compound (52%). 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.82 (d, J = 7.5 Hz, 3H), 0.85 (d, J = 7.5 Hz, 3H), 1.65 (m, 2H), 2.15 (m, 1H), 2.70 (m, 3H), 2.85 (d, 7.5 Hz, 2H), 3.08 (m, 1H), 3.18 (m, 1H), 3.30 (M, 2H), 3.60 (m, 3H), 3.80 (m, 1H), 4.16 (m, 1H), 4.40 (s, 1H), 5.16 (d, J = 9 Hz, 1H), 5.24 (s, 2H), 6.60 (d, J = 9 Hz, 1H), 7.20 (m, 10H), 7.83 (s, 1H), 8.80 (s, 1H). Mass spectrum: (M+H)$^+$ = 594.

Example 7
(2S,3S,5S)-2-(N-((5-Thiazolyl)-methoxycarbonyl)amino)-3-hydroxy-5-(2S-(1-imidazolidin-2-onyl)-3,3-dimethyl butanoyl)amino-1,6-diphenylhexane.

A. 2S-(1-Imidazolidin-2-onyl)-3,3-dimethyl butanoic acid.

Using the procedures described in Example 1J to 1M, but replacing L-valine methyl ester with L-t-butyl-leucine methyl ester provided the desired compound. 300 MHz ^{1}H NMR (DMSO-d$_6$) δ 1.0 (s, 9H), 3.22 (t, J = 7.5 Hz, 2H), 3.55 (q, J = 7.5 Hz, 1H), 3.65 (q, J = 7.5 Hz, 1H), 4.14 (s, 1H), 6.40 (s, 1H), 12.62 (br s, 1H). Mass spectrum: (M+H)$^+$ = 201.

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B.   (2S,3S,5S)-2-(N-((5-Thiazolyl)-methoxycarbonyl)amino)-3-hydroxy-5-(2S-
(1-imidazolidin-2-onyl)-3,3-dimethyl butanoyl)amino-1,6-diphenylhexane.
Coupling of the amino compound from Example 6E with the carboxylic
acid from Example 7A using standard procedure (EDAC in DMF) provided the
desired compound (77%). 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.0 (s, 9H), 1.68 (m,
2H), 2.60-2.80 (m, 3H), 2.85 (d, J = 7.5 Hz, 1H), 3.10 (m, 1H), 3.30 (m, 1H), 3.50
(m, 1H), 4.56 (s, 1H), 5.15 (d, J = 7.5 Hz, 1H), 5.25 (ABq, 1H), 6.50 (d, J = 7 Hz,
1H), 7.20 (m, 10H), 7.83 (s, 1H), 8.80 (s, 1H). Mass spectrum: (M+H)$^+$ = 609.

Example 8
(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-(2S-(1-
imidazolidin-2-onyl)-3,3-dimethyl butanoyl)amino-1,6-diphenylhexane.
Coupling of the amino compound from Example 1N with the carboxylic
acid from Example 7A using standard procedure (EDAC in DMF) provided the
desired compound (80%). 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.0 (s, 9H), 2.18 (s,
6H), 2.68 (m, 1H), 2.80 (m, 1H), 2.98 (m, 3H), 3.10 (m, 1H), 3.27 (q, J = 7 Hz,
1H), 3.53 (m, 1H), 3.77 (m, 1H), 4.0 (s, 1H), 4.20 (m, 4H), 6.72 (m, 1H), 7.0 (m,
3H), 7.10-7.25 (m, 10H). Mass spectrum: (M+H)$^+$ = 629.

Example 9
(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-(2S-(1-
imidazolidin-2-thionyl)-3-methyl butanoyl)amino-1,6-diphenylhexane.

A.   2S-(1-Imidazolidin-2-thionyl)-3-methyl butanoic acid.
Using the same procedures described in Example 1J to 1M, but
replacing 1,1-carbonyl-diimidazole with 1,1,-thiocarbonyldiimidazole provided
the desired compound. 300 MHz ^{1}H NMR (DMSO-d$_6$) δ 0.87 (d, J = 6 Hz, 3H),
0.96 (d, J = 6 Hz, 3H), 2.11 (m, 1H), 3.45 (m, 2H), 3.62 (m, 1H), 3.80 (q, J = 9 Hz,
1H), 4.80 (d, J = 10 Hz, 1H), 8.30 (s, 1H), 12.75 (br s, 1H).

B. (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-(2S-(1-imidazolidin-2-thionyl)-3-methyl butanoyl)amino-1,6-diphenylhexane.

Coupling of the amino compound from Example 1N with the carboxylic acid from Example 9A using standard procedure (EDAC in DMF) provided the desired compound (53%). 300 MHz ^{1}H NMR (CDCl3) δ 0.82 (d, J = 6 Hz, 3H), 0.93 (d, J = 6 Hz, 3H), 1.75 (m, 1H), 2.20 (s, 6H), 2.65 (m, 1H), 2.84 (m, 1H), 3.0 (m, 3H), 3.25 (m, 1H), 3.40 (m, 2H), 3.54 (d, J = Hz, 1H), 3.78 (m, 1H), 4.22 (m, 4H), 4.56 (d, J = 10.5 Hz, 1H), 5.65 (s, 1H), 6.60 (d, J = Hz, 1H), 7.0 (m, 3H), 7.25 (m, 10H). Mass spectrum: (M+H)+ = 631.

Example 10
(2S,3S,5S)-2-(4-Amino-2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-imidazolidin-2-onyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane.

A. 2,6-Dimethyl-4-nitro phenoxyacetic acid ethyl ester.

To a solution of 10.5 g (54.6 mmole) of ethyl 2,6-dimethylphenoxy acetate and 7.5 g (109 mmole) of sodium nitrite in 100 ml of methylene chloride was added 50 ml of trifluoroacetic acid slowly. The reaction mixture became solid after addition. Additional 35 ml of trifluoroacetic acid was added. After the reaction mixture was stirred at room temperature for 3 h, it was carefully partitioned between saturated sodium bicarbonate solution and methylene chloride. The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate, filtered and evaporated to dryness under reduced pressure. The residue was recrystalized in 30% ethyl acetate and hexanes to give 4.75 g (36%) of ethyl 2,6-dimethyl-4-nitro phenoxyacetate as light yellow prisms. 300 MHz ^{1}H NMR (CDCl3) δ 1.34 (3H, t, J = 7.5 Hz), 2.39 (6H, s), 4.31 (2H, q, J = 7.5 Hz), 7.93 (2H, s).

B. 2,6-Dimethyl-4-nitro-phenoxyacetic acid.

To a solution of 0.962 g (4.06 mmole) of ethyl 2,6-dimethyl-4-nitro phenoxy acetate in 10 ml of methanol was added 1 ml of 3 N sodium hydroxide.

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After the reaction mixture was stirred at room temperature for 30 minutes it was acidified with 3 N HCl and partitioned between water and methylene chloride. The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate, filtered and evaporated to dryness under recduced pressure to give 0.82 g (97%) of 2,6-dimethyl-4-nitro phenoxy acetic acid as light yellow solid. 300 MHz ^{1}H NMR (d$_3$-DMSO) δ 2.35 (6H, s), 4.55 (2H, s) 7.97 (2H, s), 13.02 (1H, bs).

C. (2S,3S,5S)-2-(t-Butyloxycarbonyl) amino-3-hydroxy-5-(2S-(1-imidazolidin-2-only)-3-methyl-butanoyl)amino-1,6-diphenylhexane.

Coupling of (2S,3S,5S)-2-(t-butyloxycarbonyl) amino-3-hydroxy-5-amino-1,6-diphenylhexane with the carboxylic acid from Example 1M using standard procedure (EDAC in DMF) provided the desired compound (100%). 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.83 (d, J = 6 Hz, 3H), 0.87 (d, J = 6 Hz, 3H), 1.40 (s, 9H), 1.70 (m, 2H), 2.16 (m, 1H), 2.58-2.80 (m, 4H), 3.10-3.30 (m, 4H), 3.65 (m, 2H), 4.20 (m, 1H), 4.38 (s, 1H), 4,83 (d, J= Hz, 1H), 6.53 (d, J = 9 Hz, 1H), 7.20 (m, 10H). Mass spectrum: (M+H)$^+$ = 553.

D. (2S,3S,5S)-2-Amino-3-hydroxy-5-(2S-(1-imidazolidin-2-onyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane.

Deprotection of the Boc-protecting group of the compound from Example 10C by standard procedure (TFA/CH$_2$Cl$_2$) provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.87 (d, J = 6 Hz, 3H), 0.90 (d, J = 6 Hz, 3H), 1.33 (dd, J = 4.5, 9.0 Hz, 1H) 2.18 (m, 1H), 2.50 (m, 1H), 2.80 (m, 5H), 3.20 (m, 4H) 3.72 (d, J = 10 Hz, 1H), 4.30 (m, 1H), 4.50 (s, 1H), 6.67 (d, J = 7 Hz, 1H), 7.20 (m, 10H). Mass spectrum: (M+H)$^+$ = 453.

E. (2S,3S,5S)-2-(4-Nitro-2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-imidazolidin-2-onyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane.

Coupling of the amino compound from Example 10D with the carboxylic acid from Example 10B using standard procedure (EDAC in DMF) provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.83 (d, 7 = Hz, 3H), 0.86 (d, J = 7 Hz, 3H), 1.70 (m, 3H), 2.18 (m, 2H), 2.28 (s, 6H) 2.75 (m, 3H), 2.95-3.30 (m,

6H), 3.67 (d, J = 10.5 Hz, 1H), 3.75 (m, 1H), 3.82 (d, J = 4 Hz, 1H), 4.25 (m, 5H), 6.55 (d, J = 7 Hz, 1H), 7.20 (m, 10H), 7.92 (s, 2H). Mass spectrum: $(M+H)^+$ = 660.

F. (2S,3S,5S)-2-(4-Amino-2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-imidazolidin-2-onyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane.

To a suspension of 7 mg of 10% Pd/C in 5 ml of methanol was added a solution of 69 mg of the compound from Example 10E. The reaction mixture was stirred vigorously under a hydrogen atmosphere (balloon filled with hydrogen attached to a 3-way stopcock). After 1 h, reaction was complete by TLC analysis; the catalyst was filtered off and the filtrate was concentrated in vacuo. The crude product was purified by silica gel column chromatography (2% to 5% MeOH/CH_2Cl_2) to provide the desired compound (65%). 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.82 (d, J = Hz, 3H), 0.87 (d, J = 6 Hz, 3H), 1.70 (m, 2H), 2.10 (s, 6H), 2.15 (m, 2H), 2.72 (m, 2H), 2.97 (d, J = 7.5 Hz, 2H), 3.08 (m, 1H), 3.15 (m, 1H), 3.30 (m, 2H), 3.45 (br s, 2H), 3.66 (d, J = 10 Hz, 1H), 3.72 (m, 1H), 3.90 (d, J = 3 Hz, 1H), 4.10-4.20 (m, 4H), 4.30 (s, 1H), 6.33 (s, 2H), 6.57 (d, J = 9 Hz, 1H), 7.20 (m, 10H). Mass spectrum: $(M+H)^+$ = 630.

Example 11
(2S,3S,5S)-2-(2,4,6-Trimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-imidazolidin-2-onyl)-3-methylbutanoyl) amino-1,6-diphenylhexane.

A. 2,4,6-Trimethylphenoxyacetic acid.

Using the procedures from Example 1G and 1H, but replacing 2,6-dimethylphenol with 2,4,6-trimethylphenol provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 2.25 (s, 9H), 4.43 (s, 2H), 6.84 (s, 2H). Mass spectrum: $(M+H)^+$ = 195.

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B. (2S,3S,5S)-2-(2,4,6-Trimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-imidazolidin-2-onyl)-3-methylbutanoyl) amino-1,6-diphenylhexane.

Coupling of the amino compound from Example 10D with the carboxylic acid from Example 11A using standard procedure (EDAC in DMF) provided the desired compound (51%). 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.82 (d, J = 6 Hz, 3H), 0.85 (d, J = 6 Hz, 3H), 1.70 (m, 4H), 2.13 (s, 6H), 2.25 (s, 3H), 2.75 (m, 2H), 2.97 (d, J = 7 Hz, 1H), 3.13 (m, 2H), 3.28 (m, 2H), 3.68 (d, J = 10 Hz, 1H), 3.72 (m, 1H), 4.16 (m, 4H), 4.40 (br s, 1H), 6.67 (d, J = 8 Hz, 1H), 6.80 (s, 2H), 7.20 (m, 10H). Mass spectrum: (M+H)$^+$ = 629.

Example 12
(2S,3S,5S)-2-(4-Fluoro-2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-imidazolidin-2-onyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane.

A. 4-Fluoro-2,6-dimethylphenoxyacetic acid.

Using the procedure from Example 1G and 1H, but replacing 2,6-dimethylphenol with 4-fluoro-2,6-dimethylphenol provided the desired compound. 300 MHz ^{1}H NMR (CD$_3$OD) δ 2.26 (s, 6H), 4.37 (s, 2H), 6.73 (d, J = 9 Hz, 2H). Mass spectrum: M$^+$ = 198.

B. (2S,3S,5S)-2-(4-Fluoro-2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-imidazolidin-2-onyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane.

Coupling of the amino compound from Example 10D with the carboxylic acid from Example 12A provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.83 (d, J = 6 Hz, 3H), 0.86 (d, J = 6 Hz, 3H), 1.72 (m, 2H), 2.15 (s, 6H), 2.20 (m, 1H), 2.76 (m, 2H), 2.98 (d, J = 7 Hz, 2H), 3.12 (m, 2H), 3.30 (m, 2H), 3.67 (d, J = 10 Hz, 1H), 3.72 (m, 1H), 4.13 (AB q, J = 8, 9 Hz, 2H), 4.20 (m, 2H), 4.37 (s, 1H), 6.64 (d, J = 9 Hz, 1H), 6.70 (d, J = Hz, 2H), 7.20 (m, 10H). Mass spectrum: (M+H)$^+$ = 633.

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Example 13
(2S,3S,5S)-2-(4,6-Dimethyl pyrimidin-5-oxy-acetyl) amino-3-hydroxy-5-(2S-(1-imidazolidin-2-onyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane.

A.   4,6-Dimethyl pyrimidin-5-oxy-acetic acid.

Using the procedures from Example 1G and 1H, but replacing 2,6-dimethylphenol with 5-hydroxy-4,6-dimethylpyrimidine (prepared according to Chem. Ber. **93** pg. 1998, 1960) provided the desired compound. 300 MHz ^{1}H NMR (DMSO-d$_6$) δ 2.45 (s, 6H), 4.55 (s, 2H), 8.50 (s, 1H). Mass spectrum: $(M+H)^+$ = 183.

B.   (2S,3S,5S)-2-(4,6-Dimethyl pyrimidin-5-oxy-acetyl) amino-3-hydroxy-5-(2S-(1-imidazolidin-2-onyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane.

Coupling of the amino compound from Example 10D with the carboxylic acid from Example 13A provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.82 (d, J = 6 Hz, 3H), 0.85 (d, J = 6 Hz, 3H), 1.70 (m, 2H), 2.15 (m, 1H), 2.40 (s, 6H), 2.75 (m, 2H),2.97 (d, J = 7 Hz, 2H), 3.12 (m, 2H), 3.30 (m, 2H), 3.66 (d, J = 10 Hz, 1H), 3.74 (m, 1H), 3.88 (d, J = Hz, 1H), 4.20 (m, 4H, 6.62 (d, J = 9 Hz, 1H), 7.0 (d, J = 9 Hz, 1H), 7.20 (m, 10H), 8.70 (s, 1H). Mass spectrum: $(M+H)^+$ = 617.

Example 14
D.   (2S,3S,5S)-2-(2,4-Dimethyl-pyridin-3-oxy-acetyl) amino-3-hydroxy-5-(2S-(1-imidazolidin-2-onyl)-3,3-dimethyl butanoyl) amino-1,6-diphenylhexane.

A.   2,4-Dimethyl-pyridin-3-oxy-acetic acid.

Using the procedures from Example 1G and 1H, but replacing 2,6-dimethylphenol with 2,4 dimethyl-3-hydroxypyridine (prepared according to J. Med. Chem. **35**, pg. 3667-3671, 1992) provided the desired compound. 300 MHz ^{1}H NMR (DMSO-d$_6$) δ 2.26 (s, 3H), 2.42 (s, 3H), 4.44 (s, 2H), 7.08 (d, J = 5 Hz, 1H), 8.07 (d, J = 5 Hz, 1H). Mass spectrum: $(M+H)^+$ = 182.

B. (2S,3S,5S)-2-(2,4-Dimethyl-pyridin-3-oxy- acetyl) amino-3-hydroxy-5-(t-butyloxycarbonyl) amino-1,6-diphenylhexane.

Coupling of the amino compound from Example1F with the carboxylic acid from Example 14A using standard procedure (EDAC in DMF) provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.40 (s, 9H), 1.70 (m, 2H), 2.18 (s, 3H), 2.40 (s, 3H), 2.77 (m, 2H), 2.98 (d, J = 7 Hz, 2H), 3.75-3.95 (m, 3H), 4.20 (s, 2H), 4.22 (m, 1H), 4.60 (br d, 1H), 7.0 (d, J = 5H, 1H), 7.10 (m, 3H), 7.25 (m, 7H), 8.16 (d, J = 5 Hz, 1H). Mass spectrum: (M+H)$^+$ = 548.

C. (2S,3S,5S)-2-(2,4-Dimethyl-pyridin-3-oxy-acetyl) amino-3-hydroxy-5-amino-1,6-diphenylhexane.

Deprotection of the Boc-group in the compound from Example 14B using standard procedure (TFA/CH$_2$Cl$_2$) provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.45 (m, 1H), 1.62 (m, 1H), 2.23 (s, 3H), 2.45 (s, 3H), 2.50 (m, 1H), 2.80 (m, 1H), 3.0 (m, 2H), 3.12 (m, 1H), 3.90 (m, 1H), 4.18 (m, 1H), 4.25 (ABq, J = 9, 12 Hz, 2H), 6.98 (d, J = 5 Hz, 1H), 7.10 (m, 2H), 7.30 (m, 8H), 8.17 (d, J = 5 Hz, 1H). Mass spectrum: (M+H)$^+$ = 448.

D. (2S,3S,5S)-2-(2,4-Dimethyl-pyridin-3-oxy-acetyl) amino-3-hydroxy-5-(2S-(1-imidazolidin-2-onyl)-3,3-dimethyl butanoyl) amino-1,6-diphenylhexane.

Coupling of the amino compound from Example 14C with the carboxylic acid from Example 7A using standard procedure (EDAC in DMF) provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.0 (s, 9H), 1.70 (m, 3H), 2.18 (s, 3H), 2.42 (s, 3H), 2.75 (m, 2H), 3.0 (m, 4H), 3.30 (m, 1H), 3.55 (m, 1H), 3.80 (m, 1H), 4.05 (s, 1H), 4.20 (m, 4H), 4.60 (s, 1H), 6.70 (d, J = 7 Hz, 1H), 6.97 (d, J = 5 Hz, 1H), 7.15 (m, 3H), 7.25 (m, 7H), 8.17 (d, J = Hz, 1H), Mass spectrum: (M+H)$^+$ = 630.

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Example 15
(2S,3S,5S)-2-(2,4-Dimethyl-pyridin-3-oxy-acetyl) amino-3-hydroxy-5-(2S-(1-imidazolidin-2-onyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane.

Coupling of the amino compound from Example 14C with the carboxylic acid from Example 1M using standard procedure (EDAC in DMF) provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.82 (d, J = 6 Hz, 3H), 0.86 (d, J = 6 Hz, 3H), 1.75 (m, 3H), 2.15 (m, 1H), 2.18 (s, 3H), 2.40 (s, 3H), 2.75 (m, 2H), 2.97 (d, J = 7.5 Hz, 2H), 3.20 (m, 4H), 3.70 (d, J - 10 Hz, 1H), 3.75 (m, 1H), 4.20 (m, 6H), 4.52 (s, 1H), 3.75 (m, 1H), 4.20 (m, 6H), 4.52 (s, 1H), 6.80 (d, J - 7 Hz, 1H), 6.96 (d, J = 4.5 Hz, 1H), 7.20 (m, 10 H), 8.17 (d, J = 4.5 Hz, 1H). Mass spectrum: (M+H)$^+$ = 616.

Example 16
(2S,3S,5S)-2-(2,6-Dimethylthiophenoxyacetyl) amino-3-hydroxy-5(2S-(1-imidazolidin-2-onyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane.

A.   2,6-Dimethylthiophenoxy acetic acid.

Using the procedures from Example 1G and 1H, but replacing 2,6-dimethylphenol with 2,6-dimethylthiophenol provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 2.56 (s, 6H), 3.40 (s, 2H), 7.10 (m, 3H). Mass spectrum: (M+H)$^+$ = 197.

B.   (2S,3S,5S)-2-(2,6-Dimethylthiophenoxyacetyl) amino-3-hydroxy-5-(2S-(1-imidazolidin-2-onyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane.

Coupling of the carboxylic acid from Example 16A with the amino compound from Example 10D provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.82 (d, J = 6 Hz, 3H), 0.86 (d, J = 6 Hz, 3H), 2.15 (m, 1H), 2.52 (s, 6H), 2.70 (m, 4H), 3.10 (m, 2H), 3.30 (m, 4H), 3.60 (m, 2H), 4.0 (m, 1H), 4.10 (m, 1H), 4.22 (s, 1H), 6.39 (d, J = 7 Hz, 1H), 6.58 (d, J = 9 Hz, 1H), 7.20 (m, 13H). Mass spectrum: (M+H)$^+$ = 631.

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Example 17
(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-pyrrolidin-2-onyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane.

A. 4-Bromobutanoyl-L-valine methyl ester.

To a solution of 1.08 g (8.4 mmole) of L-valine methyl ester in 30 ml of CH_2Cl_2 was added 1.36 ml (16.8 mmole) of pyridine, cooled to 0°C and 1.55 g (8.4 mmole) of 4-bromobutanoyl chloride added. The solution was stirred at 0°C for 40 minutes and at RT for 1 h. The solution was washed with satd. $NaHCO_3$, brine and dried with anhy. Na_2SO_4; filtered and concentrated in vacuo. The crude product was purified by silica gel column chromatography (5% EtOAc/CH_2Cl_2) to provide 1.82 g (77%) of desired product. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.92 (d, J = 6 Hz, 3H), 0.96 (d, J = 6 Hz, 3H) 2.20 (m, 3H), 2.46 (m, 2H), 3.50 (m, 2H), 3.76 (s, 3H), 4.58 (dd, J = 4,7 Hz, 1H), 5.97 (br d, J = 7 Hz, 1H). Mass spectrum: (M+H)$^+$ = 297.

B. 2S-(1-Pyrrolidin-2-onyl)-3-methyl-butanoic acid.

To a solution of 1.49 g (5.3 mmole) of the compound from Example 17A in a mixture of DMF/CH_2Cl_2 cooled to 0°C was added 0.234 g (1.1 equivalent) of 60% sodium hydride in mineral oil. The mixture was slowly warmed up to RT and stirred overnight. The mixture was poured into satd. ammonium chloride and extracted with ethyl acetate, dried and concentrated in vacuo. The crude product was hydrolyzed using lithuim hydroxide as in Example 1H to provide the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.96 (d, J = 7 Hz, 3H), 1.06 (d, J = 7 Hz, 3H), 2.10 (m, 2H), 2.40 (m, 1H), 2.50 (t, J = 7 Hz, 2H), 3.56 (m, 2H), 4.14 (d, J = 10 Hz, 1H). Mass spectrum: (M+H)$^+$ = 186.

C. (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-pyrrolidin-2-onyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane.

Coupling of the carboxylic acid from Example 17B with the amine from Example 1N using standard procedure (EDAC in DMF) provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.77 (d, J = 7 Hz, 3H), 0.83 (d, J = 7 Hz, 3H), 1.75 (m, 3H), 2.10 (m, 1H), 2.20 (s, 6H), 2.25 (m, 1H), 2.65 (m, 1H),

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2.85 (m, 1H), 3.0 (d, J = 7 Hz, 2H), 3.20 (m, 1H), 3.77 (m, 2H), 3.88 (d, J = 10 Hz, 1H), 4.20 (m, 3H), 6.30 (d, J = 7 Hz, 1H), 6.98 (m, 3H), 7.20 (m, 10 H). Mass spectrum: (M+H)+ = 614.

Example 18
(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-pyrrolidin-2,5-dionyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane.

A. 2S-(1-Pyrrolidin-2,5-dionyl)-3-methyl-butanoic acid benzyl ester.

To a solution of 700 mg (3.38 mmole) of L-valine benzyl ester in 6 ml of chloroform was added 1 equivalent of succinic anhydride. After 1 h at RT, the solvent was removed in vacuo and the residue was dissolved in 20 ml of DMF. To this solution was added 0.52 g of N-hydroxy-benzotriazole, 0.68 g of EDAC and 0.52 ml of triethylamine. After 24 h at RT, 20 mg of 4-dimethylaminopyridine was added. The solution was left at RT for 3 days. After standard work-up, the crude product was purified by silica gel column chromatography to provide 0.25 g of desired product (26%). 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.84 (d, J = 7 Hz, 3H), 1.12 (d, J = 7 Hz, 3H), 2.70 (m, 1H), 2.71 (s, 4H), 4.45 (d, J = 9 Hz, 1H), 5.15 (s, 2H), 7.30 (m, 5H).

B. 2S-(1-Pyrrolidin-2,5-dionyl)-3-methyl-butanoic acid.

A mixture of 0.245 of the product from Example 18A, 30 mg of 10% palladium on charcoal in 50 ml of methanol was stirred vigorously under hydrogen atmosphere (balloon filled with hydrogen) for 1 h. The catalyst was filtered off and the solvent was removed under vacuum to provide 168 mg of the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.84 (d, J = 6 Hz, 3H), 1.13 (d, J = 6 Hz, 3H), 2.65 (m, 1H), 2.80 (s, 4H), 4.45 (d, J = 8 Hz, 1H). Mass spectrum: (M+H)+ = 200.

C. (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-pyrrolidin-2,5-dionyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane.

Coupling of the carboxylic acid from Example 18B with the amine from Example 1N using standard procedure (EDAC in DMF) provided the desired

product (75%). 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.70 (d, J = 4 Hz, 3H), 0.72 (d, J = 4 Hz, 3H), 1.70 (m, 1H), 2.20 (s, 6H), 2.45 (m, 2H), 2.60 (s, 4H), 2.80 (m, 2H), 3.0 (m, 2H), 3.76 (m, 1H), 4.20 (m, 6H), 7.0 (m, 3H), 7.20 (m, 10H). Mass spectrum: (M+H)$^+$ = 628.

Example 19

(2S,3S,5S)-2-(Trans-3-(2,6-dimethylphenyl) propenoyl) amino-3-hydroxy-5-(2S-1-tetrahydropyrimidin-2-onyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane.

A. 2,6-Dimethyl benzaldehyde.

Oxidation of 2,6-dimethyl benzyl alcohol by standard Swern oxidation procedure (oxalyl chloride/DMSO) provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 2.62 (s, 6H), 7.10 (m, 2H), 7.33 (t, J = 7 Hz, 1H), 10.63 (s, 1H), Mass spectrum: (M+H)$^+$ = 135.

B. Trans-3-(2,6-dimethylphenyl)-propenoic acid methyl ester.

To a solution of trimethyl phosphonoacetate (149 mg, 0.82 mmole) in 15 ml of THF was added 36 mg of sodium hydride (60% in oil). After 15 minutes 100 mg of the compound from Example 19A in 2 ml of THF was added. After 2 h, the reaction was quenched carefully with water and extracted with ethyl acetate (70 ml), dried and concentrated. Purification of the crude product by silica gel column chromatography (hexane/EtOAc 95:5) provided the desired compound (75%). 300 MHz ^{1}H NMR (CDCl$_3$) δ 2.35 (s, 6 H), 3.82 (s, 3H), 6.07 (d, J = 16 Hz, 1H). 7.10 (m, 3H), 7.85 (d, J = 16 Hz, 1H). Mass spectrum: (M+NH$_4$)$^+$ = 191.

C. Trans-3-(2,6-dimethylphenyl)-propenoic acid.

Hydrolysis of the methyl ester from Example 19B using lithium hydroxide in a mixture of methanol and water provided the desired compound (84%). 300 MHz ^{1}H NMR (CDCl$_3$) δ 2.38 (s, 6H), 6.13 (d, J = 16 Hz, 1H), 7.10 (m, 3H), 7.96 (d, J = 16 Hz, 1H). Mass spectrum: (M+H)$^+$ = 194.

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D. (2S,3S,5S)-2-(Trans-3-(2,6-dimethylphenyl) propenoyl) amino-3-hydroxy-5-(t-butyloxycarbonyl) amino-1,6-diphenylhexane.

Coupling of the carboxylic acid from Example 19C with the amine from Example 1F using standard procedure (EDAC/DMF) provided the desired compound (84%). 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.40 (s, 9H), 1.68 (m, 1H), 2.34 (s, 6H), 2.75 (m, 2H), 2.96 (m, 2H), 3.72 (m, 1H), 3.85 (m, 1H), 4.08 (m, 2H), 4.60 (m, 1H), 5.88 (d, J = 10 Hz, 1H), 5.94 (d, J = 16 Hz, 1H), 7.10 (m, 5H), 7.25 (m, 8H), 7.72 (d, J = 16 Hz, 1H). Mass spectrum: (M+H)$^+$ = 543

E. (2S,3S,5S)-2-(Trans-3-(2,6-dimethylphenyl) propenoyl) amino-3-hydroxy-5-(2S-1-tetrahydropyrimidin-2-onyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane.

Removal of the Boc-protecting group of the compound from Example 19D (TFA/CH$_2$Cl$_2$) and coupling of the resulting amine with the carboxylic acid from Example 2A using standard procedure (EDAC/DMF) provided the desired compound (73%). 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.82 (d, J = 6 Hz, 3H), 0.87 (d, J = 6 Hz, 3H), 1.50 (m, 1H), 1.70 (m, 2H), 2.20 (m, 1H), 2.33 (s, 6H), 2.68 (m, 1H), 2.78 (m, 1H), 2.85 (m. 1H), 3.05 (m, 5H), 3.73 (m, 1H), 4.17 (m, 1H), 4.30 (d, J = 3 Hz, 1H), 4.60 (s, 1H), 5.95 (d, J = 15 Hz, 1H), 6.0 (d, J = 9 Hz, 1H), 6.80 (d, J = 7 Hz, 1H), 7.25 (m, 13H), 7.70 (d, J = 15 Hz, 1H). Mass spectrum: (M+H)$^+$ = 625.

Example 20

(2S,3S,5S)-2-(3-(2,6-Dimethylphenyl) propanoyl) amino-3-hydroxy-5-(2S-(1-tetrahydropyrimidin-2-onyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane.

A. 3-(2,6-Dimethylphenyl) propanoic acid methyl ester.

A solution of 400 mg of the compound from Example 19B in 25 ml of methanol and 40 mg of 10% Pd/C was stirred vigorously under a hydrogen atmosphere (balloon pressure) for 3 h. The catalyst was filtered off and

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concentration of the filtrate in vacuo provided the desired compound (98%). 300 MHz ^{1}H NMR (CDCl$_3$) δ 2.35 (s, 6H), 2.45 (m, 2H), 2.98 (m, 2H), 3.22 (s, 3H), 7.02 (s, 3H). Mass spectrum: (M+H)$^+$ = 210.

B. 3-(2,6-Dimethylphenyl) propanoic acid.

Hydrolysis of the methyl ester from Example 20A, using lithium hydroxide in methanol and water provided the desired compound (93%). 300 MHz ^{1}H NMR (CDCl$_3$) δ 2.36 (s, 6H), 2.50 (m, 2H), 3.0 (m, 2H), 7.03 (s, 3H). Mass spectrum: (M+NH$_4$)$^+$ = 196.

C. (2S,3S,5S)-2-(3-2,6-Dimethylphenyl) propanoyl) amino-3-hydroxy-5-(t-butyloxycarbonyl) amino-1,6-diphenylhexane.

Coupling of the carboxylic acid from Example 20B with the amine from Example 1F using standard coupling procedure (EDAC/DMF) provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.40 (s, 9H), 1.55 (m, 2H), 2.20 (m, 2H), 2.30 (s, 6H), 2.74 (m, 2H), 2.85 (m, 4H), 3.66 (m, 1H), 3.82 (m, 1H), 3.95 (m, 2H), 4.57 (br d, 1H), 5.66 (d, J = 9 Hz, 1H), 7.0 (s, 3H), 7.22 (m, 10H). Mass spectrum: (M+H)$^+$ = 545.

D. (2S,3S,5S)-2-(3-(2,6-Dimethylphenyl) propanoyl) amino-3-hydroxy-5-(2S-(1-tetrahydropyrimidin-2-onyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane.

Removal of the Boc-protecting group of the compound from Example 20C using trifluoroacetic acid in CH$_2$Cl$_2$ and coupling of the resulting amine with the carboxylic acid from Example 2A using standard coupling procedure (EDAC/DMF) provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.82 (d, J = 6 Hz, 3H), 0.86 (d, J = 6 Hz, 3H), 1.55 (m, 2H), 1.65 (m, 1H), 1.70 (s, 3H), 2.20 (m, 3H), 2.30 (s, 6H), 2.65 (m, 1H), 2.75 (m, 1H), 2.86 (m, 5H), 3.10 (m, 3H), 3.68 (m, 1H), 4.10 (m, 4H), 4.63 (s, 1H), 5.75 (d, J = 7 Hz, 1H), 6.76 (d, J = 7 Hz, 1H), 7.0 (m, 3H), 7.20 (m, 10H). Mass spectrum: (M+H)$^+$ = 627.

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Example 21
(2S,3S,5S)-2-(2,6-Dimethyl-4-hydroxy-phenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydropyrimidin-2-onyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane.

A. 2,6-Dimethyl-4-tert-butyldimethylsilyloxy phenol

To a solution of 2.5 g (14.7 mmole) of 2,6-dimethylquinone in 5 ml of methanol was added 200 mg of Pd/C (20%). The reaction mixture was stirred under 1 atmosphere of hydrogen for overnight. The Pd/C was removed over a celite pad, and the solvent was evaporated to dryness under reduced pressure to give 2.0 g (100%) of 2,6-dimethyldihydroquinone as a light yellow oil.

To a solution of 2.0 g (14.7 mmole) of 2,6-dimethyldihydroquinone in 10 ml of methylene chloride was added 1.2 g (17.6 mmole) of imidazole and 2.2 g (14.7 mmol) of tert-butyldimethylsilyl chloride subsequently at 0°C. After the reaction was complete as indicated by TLC, it was partitioned between methylene chloride and 1:1 mixture of 3 N hydrogen chloride and brine. The organic layer was washed with brine, dried over sodium sulfate, filtered and evaporated to dryness under reduced pressure. Silica gel chromatography using 5% ethyl acetate:hexanes gave 1.8 g (49%) of 2,6-dimethyl-4-tert-butyldimethylsilyloxy phenol as a white solid. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.16 (s, 6H), 0.98 (s, 9H), 2.19 (s, 6H), 4.22 (s, 1H), 6.48 (s, 2H). Mass spectrum: $(M+H)^+ = 253$.

B. Ethyl 2,6-Dimethyl-4-tert-Butyldimethylsilyloxy phenoxyl acetate

A solution of 1.8 g (7.1 mmole) of 2,6-dimethyl-4-tert-butyldimethylsilyloxy phenol in 5 ml of dimethylformamide was treated with 2.0 g (1.43 mmole) of potassium carbonate and 830 µl (7.5 mmole) of ethyl bromoacetate. The resulting solution was heated at 70°C for 4 hr. After cooled to room temperature, the reaction mixture was partitioned between ethyl acetate and 3 N hydrogen chloride. The combined organic layer was washed with diluted brine, dried over magnesium sulfate, filtered, and evaporated in vacuo. Silica gel chromatography using 5% ethyl acetate:hexanes gave 2.03 g (85%) of ethyl 2,6-dimethyl-4-tert-butyldimethylsilyloxy phenoxyl acetate as a

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light yellow oil. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.17 (s, 6H), 0.97 s, 9H), 1.33 (t, 3H, J = 6.3 Hz), 2.22 (s, 6H), 4.30 (q, 2H, J = 6.3 Hz), 4.35 (s, 2H), 6.57 (s, 2H). Mass spectrum: (M+H)$^+$ = 356.

C. 2,6-Dimethyl-4-Hydroxyl phenoxyacetic acid

To a solution of 2.03 g (6.0 mmole) of ethyl 2,6-dimethyl-4-tert-butyldimethysilyloxy phenoxy acetate in 10 ml of methanol was added 4 ml of 3 N sodium hydroxide. After the reaction mixture was stirred at room temperature for 30 minutes it was acidified with 3 N HCl. The reaction was allowed to stir for additional 1 h, and then partitioned between water and methylene chloride. The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate, filtered, and evaporated to dryness under reduced pressure. Trituration with hexanes gave 910 mg (77%) of 2,6-dimethyl-4-hydroxyl phenoxyacetic acid as a white solid. 300 MHz ^{1}H NMR (CD$_3$OD) δ 2.18 (s, 6H), 4.31 (s, 2H), 6.41 (s, 2H). Mass spectrum: (M+H)$^+$ = 214.

D. (2S,3S,5S)-2-(2,6-Dimethyl-4-hydroxy-phenoxyacetyl) amino-3-hydroxy-5-(t-butyloxycarbonyl) amino-1,6-diphenylhexane.

Coupling of the carboxylic acid from Example 21C with the amine from Example 1F using standard coupling procedure (EDAC/DMF) provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.40 (s, 9H), 1.68 (m, 2H), 2.07 (s, 6H), 2.77 (d, J = 6 Hz, 2H), 2.98 (m, 2H), 3.74 (m, 1H), 3.90 (m, 1H), 4.10 (m, 3H), 4.58 (m, 1H), 5.20 (m, 1H), 6.44 (s, 2H), 7.10-7.30 (m, 10H).

E. (2S,3S,5S)-2-(2,6-Dimethyl-4-hydroxy-phenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydropyrimidin-2-onyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane.

Removal of the Boc-protecting group of the compound from Example 21D using TFA/CH$_2$Cl$_2$ and coupling of the resulting amine with the carboxylic acid from Example 2A using standard procedure (EDAC/DMF) provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.78 (d, J = 5 Hz, 3H), 0.81 (d, J = 5 Hz, 3H), 1.47 (m, 1H), 2.03 (s, 6H), 2.18 (m, 1H), 2.62 (m, 1H), 2.80 (m, 2H), 3.05 (m, 6H), 3.78 (m, 1H), 4.12 (M, 6H), 4.37 (M, 1H), 4.71 (s, 1H), 6.47 (s, 2H), 6.94 (br d, 1H), 7.20 (m, 10H). Mass spectrum: (M+H)$^+$ = 645.

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Example 22

(2S,3S,5S)-2-(cis(±)-1,1-dioxo-2-isopropyl-3-tetrahydrothiophenoxy)amino-3-hydroxy-5-(2S-(1-tetrahydropyrimid-2-onyl)-3-methyl butanoyl)amino-1,6-diphenylhexane.

A. Cis (±)-2-isopropyl-3-hydroxy-tetrahydrothiophene.

To a solution of ethyl-3-mercaptopropionate (27.25 ml, 0.246 mole) in 200 ml of ethanol was added carefully sodium ethoxide (16.75 g, 0.246 mole) in several portions. The resulting suspension was then cooled to -20°C and ethyl-2-bromoisovalerate (50 g, 0.239 mole) in 50 ml of ethanol was added dropwise over 2 h. After addition was complete, the reaction was warmed to ambient temperature and stirred for 3 h. The mixture was poured into 600 ml of ethyl acetate and 600 ml of saturated NH_4Cl. The ethyl acetate layer was removed and the aqueous layer extracted (2 x 200 ml) with ethyl acetate. The combined organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to give an orange oil. The oil was dissolved in 500 ml of toluene and sodium ethoxide (16.75 g, 0.246 mole) was added. The reaction mixture was heated to reflux for 6 h, cooled to RT, and then poured into an ice-cold solution of 1N HCl (235 ml) and extracted with ethyl acetate (3 x 150 ml). The combined organic layers were dried over sodium sulfate, filtered and concentrated to an oil that was used in the next step without purification.

The crude product was added to 500 ml of aqueous 10% sulfuric acid and the resulting mixture heated to reflux for several hours, and then cooled to RT and neutralized with 6N sodium hydroxide and extracted with ethyl acetate (3 x 300 ml). The combined organic layer was dried, filtered and concentrated in vacuo to give a dark burgundy oil. The crude product (ketone) was purified by vacuum distillation at 75°-80°C. 300 MHz ^1H NMR ($CDCl_3$) δ 0.93 (d, J = 9 Hz, 3H), 1.03 (d, J = 9 Hz, 3H), 2.32 (m, 1H), 2.55-2.70 (m, 2H), 2.93 (t, J = 7.5 Hz, 2H), 3.38 (d, J = 4 Hz, 1H). Mass spectrum: $(M+H)^+ = 145$.

To a stirred solution of the above ketone in 125 ml of CH_2Cl_2 at 0°C was added diisobutylaluminum hydride (86 ml, 1M in THF) dropwise over 20

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minutes. The reaction mixture was allowed to warm to room temperature and then was quenched by cautious addition of 1N HCl (255 ml). The reaction mixture was extracted with ether (3 x 150 ml) and the combined ether solution was washed with satd. sodium bicarbonate, brine and dried over magnesium sulfate. The solution was concentrated in vacuo and the resulting oil was purified by silica gel column chromatography (10% EtOAc/hexane). 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.03 (d, J = 7 Hz, 3H), 1.08 (d, J = 7 Hz, 3H), 1.80 (d, J = 9 Hz, 1H), 1.90 (m, 2H), 2.24 (m, 1H), 2.90-3.10 (m, 3H), 4.36 (m, 1H). Mass spectrum: (M+H)$^+$ = 147.

B.   Cis(±)-(2-isopropyl-3-thiophenyl)-2(2-pyridyl)carbonate.

To the product from Example 22A (2.29 g, 15.7 mmole) in 40 ml of CH$_2$Cl$_2$ was added diisopropylethyl amine (4.65 ml, 26.7 mmole) and di-(2-pyridyl)carbonate (5.42 g, 25.1 mmole). After 18 h at RT, the reaction mixture was diluted with chloroform and washed sequentially with 10% citric acid, satd. sodium bicarbonate, brine and then dried over sodium sulfate; filtered and concentrated in vacuo. Purification of the crude product by silica gel column chromatography (20% EtOAc/hexane) provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.05 (d, J = 7 Hz, 3H), 1.08 (d, J = 7 Hz, 3H), 1.90 (m, 1H), 2.05 (m, 2H), 2.58 (dd, J = 6, 15 Hz, 2H), 3.10 (m, 2H), 3.28 (dd, J = 3, 12 Hz, 1H), 5.47 (m, 1H), 7.12 (m, 1H), 7.27 (m, 1H), 7.80 (m, 1H), 8.41 (m, 1H). Mass spectrum: (M+H)$^+$ = 268.

C.   (2S, 3S, 5S)-2-(cis(±)-2-Isopropyl-3-tetrahydrothiophenoxy)amino-3-hydroxy-5-(t-butyloxycarbonyl)amino-1,6-diphenylhexane.

To a solution of the compound from Example 22B (500 mg, 1.87 mmole) in 5 ml of CH$_2$Cl$_2$ was added the amine from Example 1F (791 mg, 2.06 mmole). The reaction was stirred at RT until all the compound from Example 22B was consumed. The reaction mixture was diluted with chloroform and washed with 10% citric acid, satd. sodium bicarbonate, brine and then dried with sodium sulfate; filtered and concentrated in vacuo. Purification of the crude product by silica gel column chromatography (2% MeOH/CH$_2$Cl$_2$) provided the desired compound (73%). 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.83-1.05 (m, 6H), 1.40 (s, 9H), 1.90 (m, 3H), 2.20 (m, 1H), 2.75 (m, 2H), 2.85 (m,

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4H), 2.95-3.15 (m, 3H), 3.67-3.90 (m, 4H), 4.55 (m, 1H), 5.10 (m, 1H), 5.30 (m, 1H), 7.10-7.26 (m, 10H). Mass spectrum: $(M+H)^+ = 557$.

D.   (2S,3S,5S)-2-(cis(±)-1,1-Dioxo-2-isopropyl-3-tetrahydrothiophenoxy)amino-3-hydroxy-5-(t-butyloxycarbonyl)amino-1,6-diphenylhexane.

To the compound from Example 22C (523 mg, 0.91 mmole) in 10 ml of acetone and 0.5 ml of water was added Oxone (839 mg, 1.37 mmole) and sodium bicarbonate (152 mg, 1.82 mmole). The resulting solution was stirred for 2 h, at which time a white precipitate appeared. The reaction was quenched with aqueous sodium bisulfite and extracted with ethyl acetate (2 x 100 ml), dried with sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by silica gel column chromatography (2% MeOH/CH_2Cl_2) to provide 422 mg of product. 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.20 (m, 6H), 1.40 (s, 9H), 1.60 (m, 4H), 2.10-2.32 (m, 4H), 2.67 (m, 2H), 2.75 (m, 2H), 2.85 (m, 2H), 3.15 (m, 2H), 3.70-3.90 (m, 3H), 4.56 (m, 1H), 5.30 (m, 2H), 7.10-7.30 (m, 10H).

E.   (2S,3S,5S)-2-(cis(±)-1,1-Dioxo-2-isopropyl-3-tetrahydrothiophenoxy)amino-3-hydroxy-5-(2S-(1-tetrahydropyrimid-2-onyl)-3-methyl butanoyl)amino-1,6-diphenylhexane.

Removal of the Boc-protecting group of the compound from Example 22D using TFA/CH_2Cl_2 and coupling of the resulting amine with the carboxylic acid from Example 2A provided the desired compound (82%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.82 (m, 6H), 1.0-1.20 (m, 6H), 1.60 (, 2H), 2.07 (m, 1H), 2.25 (m, 2H), 2.65-3.20 (m, 12H), 3.70 (m, 1H), 3.90 (m, 1H), 4.10-4.20 (m, 2H), 5.07 (m, 1H), 5.37 (m, 1H), 5.87-5.98 (m, 1H), 6.95-7.05 (m, 1H), 7.20 (m, 10H). Mass spectrum: $(M+H)^+ = 671$.

Example 23

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(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-dihydropyrimid-2,4-dionyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane.

A. N-(2-Ethoxyacryloyl)-N'-(1S-carbomethoxy-2-methyl-propyl)-urea.

To 1.74 g (0.013 mole) of 2-ethoxy-acryloyl chloride in 18 ml of toluene was added 3.90 g (0.026 mole) of silver cyanate. The mixture was heated to reflux for 0.75 h. The mixture was allowed to cool to RT and the precipitate allowed to settle. The supernatant (9.6 ml) was withdrawn and added to 18 ml of dry DMF and 5 ml of Et$_2$O, cooled to -15°C for 45 minutes and left in freezer overnight. The solvent was evaporated in vacuo and the residue was purified by silica gel column chromatography (2% MeOH/CH$_2$Cl$_2$) to provide 1.59 g of desired compound (90.2%). 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.96 (d, J = 7 Hz, 3H), 1.0 (d, J = 7 Hz, 3H), 1.37 (t, J = 7.5 Hz, 3H), 2.25 (m, 1H), 3.74 (s, 3H), 3.97 (q, J = 7.5 Hz, 2H), 4.42 (dd, J = 4.5, 8.0 Hz, 1H), 5.25 (d, J = 12 Hz, 1H), 7.68 (d, J = 12 Hz, 1H), 8.55 (s, 1H), 9.10 (d, J = 8 Hz, 1H). Mass spectrum: (M+H)$^+$ = 273.

B. 2S-(1-Dihydropyrimid-2,4-dionyl)-3-methyl butanoic acid.

A solution of 174 mg (0.64 mmole) of the compound from Example 23A in 10 ml of 2N sulfuric acid was refluxed for 2 h, cooled to RT and left in freezer overnight. The mixture was concentrated and the residue was extracted with ethyl acetate (2 x 100 ml), dried and concentrated in vacuo to give 122 mg of desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.06 (d, J = 7 Hz, 3H), 1.13 (d, J = 7 Hz, 3H), 2.25 (m, 1H), 5.04 (d, J = 10 Hz, 1H), 5.74 (d, J = 7 Hz, 1H), 7.50 (d, J = 10 Hz, 1H), 8.43 (s, 1H).

C. (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-dihydropyrimid-2,4-dionyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane.

Coupling of the carboxylic acid from Example 23B with the amine from Example 1N using standard coupling procedure (EDAC in DMF) provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.81 (d, J = 7 Hz, 3H), 0.92 (d, J = 7 Hz, 3H), 2.18 (s, 6H), 2.23 (m, 1H), 2.63 (m, 1H), 2.85 (m, 1H), 3.0 (m, 2H), 3.78 (m, 1H), 4.20 (m, 4H), 4.58 (d, J = 10 Hz, 1H), 5.68 (dd, J = 1.5, 7.5 Hz, 1H),

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7.0-7.25 (m, 13H), 7.50 (d, J = 7.5 Hz, 1H), 9.50 (s, 1H). Mass spectrum: $(M+H)^+ = 640$.

Example 24
Alternate Preparation of (2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane.

A. 2,6-Dimethylphenoxyacetic acid

2,6-Dimethylphenol (102.8 g, 0.842 mol) and chloroacetic acid (159.6 g, 1.68 mol) in 1000 ml of H_2O was added to a 3-L, 3-necked round bottom flask with mechanical stirring and a water-cooled condenser. A solution of NaOH (134.9 g, 3.37 mol) dissolved in 500 ml of water was slowly added to the above mixture via addition funnel and heat to reflux. After 2 hours, additional chloroacetic acid (79.4 g, 0.84 mol) and NaOH solution (67.2 g, 1.68 mol in in 200 ml water) was added to the reaction mixture. After 19 hours, additional chloroacetic acid (39.8 g, 0.42 mol) and NaOH solution (33.6 g, .84 mol in in 100 ml water) was added to the reaction mixture and refluxing was continued until starting phenol was consumed. The reaction flask was cooled in and ice-water bath and acidified to pH=1 with conc. HCl, causing a precipitate to form. The resulting slurry was stirred in the ice bath for 1 hour then filtered. The solid was dissolved in hot (100°C) water and cooled to crystallize the product as white plates, mp= 136-137°C, yield = 78.8 g, 52%.

B. (2S, 3S, 5S) -2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane.

Oxallyl chloride (36.3 ml, 0.42 mol) was added to a slurry of 2-6 dimethylphenoxyacetic acid (50 g, 0.28 mol) in 500 ml toluene followed by addition of 5 drops of DMF and stirred at room temperature for 30 min, then at 55°C for 1.5 hours. The toluene was removed on a rotary evaporator and remaining volatiles were removed in vacuo to afford 2,6-dimethyl-phenoxyacetyl chloride as an amber oil, 55 grams, 100%.

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[2S,3S,5S]-2-Amino-3-hydroxy-5-t-butyloxycarbonylamino-1,6-diphenylhexane x 0.5 succinate (111.9 g, 0.25 mol) was charged to a 2L, 3-necked round-bottomed flask with mechanical stirring. $NaHCO_3$ (106 g, 1.26 mol), 600 ml H_2O and 600 ml EtOAc were added and stirred vigorously until all solids were dissolved (15 minutes). Stirring was slowed and a solution of the 2,6-dimethyl-phenoxyacetyl chloride and EtOAc (100 ml) was added in a narrow stream via addition funnel. After 30 min of stirring, starting materials were consumed (HPLC analysis) and the layers were separated. The aqueous layer was extracted with EtOAc, the organic layers were combined and washed with 200 ml of 1 M NaOH, 200 ml of 10% HCl, 200 ml of brine, dried over $MgSO_4$, filtered and concentrated to provide the desired product as a white solid.

C. (2S, 3S, 5S) -2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-amino-1,6-diphenylhexane.

(2S, 3S, 5S) -2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane (175.1 g, 0.32 mol) and 500 ml CH_2Cl_2 were mixed with stirring. CF_3CO_2H (249 ml, 3.2 mol) was added and stirred 20-25 minutes, then the reaction mixture was poured into a separatory funnel containing 1000 ml of water and 200 ml of CH_2Cl_2. The resulting mixture was shaken carefully and the layers were separated. The organic layer was washed again with 500 ml of water, then 3x 500 ml of $NaHCO_3$ and finally 500 ml of brine. The organic solution was dried over $MgSO_4$, filtered and concentrated to a golden oil that pulled into a foam 300 ml of diethyl ether was added to the crude product and shaken vigorously to dissolve. Within minutes solid began to crystallize and the mixture became thick. Enough diethyl ether was added to make the mixture stirrable and the mixture was stirred at room temperature for 1 hour. The solid was filtered and air dried to give the desired product as 115 g of white needles, 81% yield.

A solution of HCl/diethyl ether was added to the filtrate to precipitate the remaining product as the HCl salt. This pinkish solid was collected by filtration, taking care to keep the solid flooded with N_2 while it was wet with ether. When

dry, transfered the amine salt to a separatory funnel and extracted with CH_2Cl_2 and $NaHCO_3$ (aq). The organic layer was washed with brine, dried over $MgSO_4$, concentrated and treated as above to afford an additional 15 g of the desired product, the total yield is 91%.

D. N-Carbonylbenzyloxy-3-aminopropanol

To a 12L 3-neck round bottom flask was added isopropyl acetate (6.5L). The solvent was cooled to 0^oC in an ice-water bath and 3-amino-1-propanol (1.14Kg, 15.1mol, 2.15eq) was added in one portion. To this rapidly stirring solution, benzyl chloroformate (1.20Kg, 7.03mol, 1.0eq) was added dropwise over 2h while maintaining the internal temperature of the flask between 10^oC and 15^oC. After the addition was complete, the reaction mixture was allowed to stir between 10^oC and 15^oC for an additional 0.3h after which time water (3.5L) was added in one portion. The solution was then partitioned and washed with an additional 2X3.5L of water. The organic layer was dried over potassium carbonate and concentrated to give a solid that was dissolved in excess isopropyl acetate and precipitated from solution by adding the compound to heptane. The solid was filtered under nitrogen to yield 1.20Kg (82%) of the desired product as a colorless solid.

E. N-Carbonylbenzyloxy-3-aminopropanal

335 mL of dimethylsulfoxide and 9L of methylene chloride were combined and chilled to -48^oC. 313 mL of oxalyl chloride was added over 25 minutes so that the temperature remained below -40^oC. Cooled to -48^oC, and added 500 grams of N-Cbz-3-amino-1-propanol dissolved in 1L of methylene chloride so that the temperature remained below -40^oC. Stirred for an additional hour at -45^oC. 1325 mL of triethylamine was added at such a rate that the temperature remained below -40^oC. After stirring an additional 15 minutes at -40^oC, the mixture was allowed to warm to -30^oC, then added 2.5L of 20% aqueous potassium dihydrogen phosphate. Stirred for one hour, then separated the layers, washed the organic layer with brine, and dried with

magnesium sulfate. The resulting aldehyde was kept in solution at -20°C until needed.

F. N-(N-(Benzyloxycarbonyl-3-amino)-propyl) valine methyl ester.

To a 5L 3-neck round bottom flask was added the crude (unchromatographed) product of Example 24E (115g, 0.555mol, 1.0eq) followed by addition of water (400mL) and methanol (1600mL). The reaction mixture was maintained at 25°C throughout the course of the reaction. After the solution became homogeneous, (S)-Valine methyl ester hydrochloride (90.2g, 0.538mol, 0.97eq) was added in one portion followed by rapid addition of sodium acetate trihydrate (151g, 1.11mol, 2.0eq) and sodium cycanoborohydride (73.2g, 1.17mol, 2.1eq) in said order. The reaction mixture was allowed to stir at room temperature for 0.5h and was concentrated in vacuo to remove all methanol present. To this solution, saturated aq sodium bicarbonate (400mL) was added and the mixture was extracted with isopropyl acetate (1L). The organic layer was washed with water (2X400mL), dried over sodium sulfate, and concentrated to yield 150g of crude product, which was dissolved in isopropyl acetate (300mL) and heptane (2400mL). Dry HCl was bubbled in and an oily solid precipitated out of solution. The liquid was decanted away from the solid and was dissolved in dichloromethane (3L). The solution was washed with water (600mL) and saturated aq sodium bicarbonate (600mL) and dried over sodium sulfate. It was concentrated in vacuo to yield 105g (59%) of the desired product as a light yellow oil.

G. N-(3-amino)-propyl) valine methyl ester.

To a 3L flask was added the product of Example 24F (120g, 0.372mol) and methanol (1L). This solution was allowed to stir in the presence of Raney Nickel (180g) for 1h . After removal of Raney Nickel by filtration, Pd(OH)2 (24g) was added and the solution was allowed to stir under 60 psi of a hydrogen atmosphere for 12h. The solution was purged with nitrogen and repressurized with 60 psi of hydrogen for an additional 1h. The solution was filtered and concentrated to give 63g of an oil (90%). To this oil toluene (120mL) was

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added and the solution was again concentrated in vacuo to give the desired product.

H. 2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoic acid methyl ester.

To a 5L 3-neck round bottom flask with stir bar was added the crude product of Example 24G (150g, 0.8mol) and dichloromethane (3.2L). Carbonyldiimidazole (232g, 1.44mol, 1.8eq) was added slowly in portions over 25 min. The solution was allowed to stir at ambient temperature for 40h. Water (200mL) was added over 1h with careful stirring until no more gas evolution occurred. A solution of 35% HCl was slowly added to the stirring solution until the solution became acidic. The solution was then partitioned and was washed with water (2X300mL). The organic layer was dried over sodium sulfate and was concentrated to yield 126g (74%) of the desired product as a colorless solid.

I. 2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoic acid methyl ester.

To a 12L 3-neck round bottom flask with stir bar was added the product of Example 24H (126g, 0.588mol), water (1.3L), and THF(3.9L). The solution was cooled to 0°C in an ice-water bath and lithium hydroxide monohydrate (74g, 1.76mol, 3.0eq) was added in one portion with rapid stirring. The solution was allowed to stir at 0°C for 14h. It was then acidified to pH 11 by slow addition of 50% aq phosphoric acid and the THF was removed in vacuo. The aqueous phase was washed with isopropyl acetate (2L) and was subsequently acidified to pH by slow addition of 35% aq HCl. The aqueous layer was then extracted with ethyl acetate (5X2.2L). The combined organic layers were concentrated to give the desired product (105g) as a white solid. The compound was then purified by addition of isopropyl acetate (500mL) and ethanol (15mL) and bringing the solution to a boil with rapid stirring until 50mL of solvent had evaporated. The solution was cooled to 0°C and filered to give 92g (75%) of pure desired product.

J. (2S, 3S, 5S)-2-(2.6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane.

In a 2L, 3-necked round-bottomed flask were combined the product of Example 24C (100 g, 0.22 mol), the product of Example 24I (44.8 g, 0.22 mol) and 750 ml DMF and the mixture was cooled in an ice/water bath. HOBT (90.9 g, 0.67 mol), EDAC (86 g, 0.45 mol) and triethylamine (62.5 ml, 0.45 mol) were added and the ice bath was removed, allowing the reaction mixture to stir with warming to room temperature for 5h. The reaction was diluted with 1000 ml of IPAC and quenched with 1000 ml of water. The mixture was shaken and separated, the aq. layer was extracted 1x 400 ml IPAC, the organics were washed with 1x 400 ml 10% HCl, 1x 500 ml NaHCO3, diluted with 100 ml hexanes, then washed 4x 500 ml water, and 1x 500 ml brine, dried over MgSO4, filtered and concentrated to provide the desired product as a white foam.

Example 25
(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2,4-dionyl)-3-methylbutanoyl]amino-1,6-diphenylhexane.

A. N-(2-Carbomethoxy) ethyl-L-Valine t-butyl ester.

To a solution of 1.73 g of L-Valine t-butyl ester in 10 ml of methanol was added 9.0 ml of methyl acrylate. The solution was heated to reflux overnight. Another 9.0 ml of methyl acrylate was added and continued the reflux for 24 h. The solvent was evaporated in vacuo and the crude product was purified by silica gel column chromatography (20% ethyl acetate in hexane) to provide 2.435 g of desired compound (93.9%). 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.91 (d, J=3.5 Hz, 3H), 0.93 (d, J=3.5 Hz, 3H), 1.47 (s, 9H), 1.85 (m, 1H), 2.47 (t, J=7 Hz, 2H), 2.68 (m, 1H), 2.81 (d, J=6 Hz, 1H), 2.95 (m, 1H), 3.68 (s, 3H). Mass spectrum: (M+H)$^+$ = 260.

B. N-(2-Carboxamido) ethyl-L-Valine t-butyl ester.

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To a solution of 1.86 g of the product from Example 25A in 5 ml of THF
was added 0.415 g of lithium hydroxide monohydrate in 10.8 ml of water.
After 40 min, 10.8 ml of 1N HCl was added. The reaction mixture was
evaporated to dryness and dry pyridine was added and evaporated to dryness
two times. The residue was dissolved in 25 ml of acetonitrile and 0.62 ml of
dry pyridine added. To this solution was added 2.02 g of N,N'-disuccinimidyl
carbonate. The reaction mixture was stirred for 3.5 h. The solvent was
removed in vacuo and 90 ml of THF added followed by 1.43 ml of conc.
ammonium hydroxide. The reaction was allowed to go overnight. The reaction
mixture was filtered and the filtrate concentrated in vacuo. The residue was
dissolved in ethyl acetate and washed with sodium bicarbonate, brine and
dried with anhy. sodium sulfate. After filtering off the drying agent, the filtrate
was conc. in vacuo and the crude product was purified by silica gel column
chromatography (5% MeOH in CH_2Cl_2) to give 1.19 g (68%) of desired
compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.95 (d, J=7 Hz, 3H), 0.97 (d,
J=7 Hz, 3H), 1.48 (s, 9H), 1.93 (m, 1H), 2.37 (m, 2H), 2.65 (m, 1H), 2.95 (m,
2H), 5.30 (br s, 1H), 7.85 (br s, 1H). Mass spectrum: (M+H)$^+$=245.

C. 2S-(1-Tetrahydro-pyrimid-2,4-dionyl)-3-methylbutanoic acid t-butyl ester.

A solution of 0.92 g of the product from Example 25B in 10 ml of THF
and 1.83 g of carbonyldiimidazole (CDI) was refluxed for 26 h. Then 1.83 g
of CDI was again added and the solution was refluxed for 72 h more. The
solvent was evaporated in vacuo and the residue was dissolved in ethyl
acetate and washed with water, satd. sodium bicarbonate, dilute hydrochloric
acid and then brine. The organic layer was dried, filtered and conc. in vacuo.
The crude product was purified by silica gel column chromatography (2% to 5%
MeOH in CH_2Cl_2) to give 0.54 g (52%) of desired compound. 300 MHz
^{1}H NMR (CDCl$_3$) δ 0.96 (d, J=7 Hz, 3H), 1.05 (d, J=7 Hz, 3H), 1.48 (s, 9H),
2.20 (m, 1H), 2.66 (m, 2H), 3.43 (m, 1H), 3.75 (m, 1H), 4.63 (d, J=9 Hz, 1H),
7.35 (br s, 1H). Mass spectrum: (M+H)$^+$=271.

D. 2S-(1-Tetrahydro-pyrimid-2,4-dionyl)-3-methylbutanoic acid.

A solution of 0.53 g of the compound from Example 25C in 5 ml of
trifluoroacetic acid was stirred at 0°C for 1.25 h. Solvent was evaporated in

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vacuo, dried and purified by silica gel column chromatography (2% MeOH/4% HOAc in CH_2Cl_2) to give 0.36 g of desired compound. 300 MHz ^{1}H NMR (DMSO-d$_6$) δ 0.86 (d, J=7 Hz, 3H), 0.97 (d, J=7 Hz, 3H), 2.15 (m, 1H), 3.40 (m, 4H), 4.39 (d, J=10 Hz, 1H). Mass spectrum: $(M+H)^+$=215.

E. (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2,4-dionyl)-3-methylbutanoyl] amino-1,6-diphenylhexane.

Coupling of the amino compound from Example 1N with the acid from Example 25D using standard coupling procedure (EDAC in DMF) provided the desired compound (68%). 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.83 (d, J=7Hz, 3H), 0.88 (d, J=7Hz, 3H), 1.80 (m, 2H), 2.20 (s, 6H), 2.40 (m, 1H), 2.58 (m, 1H), 2.80 (m, 1H), 2.92 (m, 1H), 3.05 (m, 3H), 3.65 (d, J=5Hz, 1H), 3.83 (m, 1H), 4.20 (m, 5H), 6.18 (d, J=9Hz, 1H), 7.0-7.38 (m, 14H). Mass spectrum: $(M+H)^+$=643.

Example 26
(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5[2S-(4-aza-1-tetrahydro-pyrimid-2-onyl)-3-methyl-butanoyl]amino-1,6-diphenylhexane.

A. N(1)-t-butyloxycarbonyl-N(2)-allyl hydrazine.

To a solution of 18.18 g of t-butyloxycarbonyl protected hydrazine in 50 ml of acetonitrile was added 19.0 g of potassium carbonate, followed by 11.9 ml of allyl bromide. The reaction mixture was heated at reflux for a total of 3 h , filtered and conc. in vacuo. The residue was dissolved in ethyl acetate and washed with satd. sodium bicarbonate and dried with anhydrous sodium sulfate and filtered. After concentration in vacuo, the crude product was purified by silica gel column chromatography (20% EtOAc/hexane) to give 4.47 g of desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.45 (s, 9H), 3.46 (m, 2H), 4.0 (br s, 1H), 5.10 (m, 2H), 5.83 (m, 1H), 6.0 (br s, 1H). Mass spectrum: $(M+H)^+$=173.

B. N(1)-t-butyloxycarbonyl-N(2)-allyl-N(2)-benzyloxycarbonyl hydrazine.

To a solution of 4.8 g of the compound from Example 26A in 15 ml of DMF was added 4.69 g of benzyloxycarbonyloxy-succinimide. The reaction mixture was stirred at RT for 72 h and the solvent was evaporated in vacuo.

The residue was dissolved in ethyl acetate, washed with satd. sodium bicarbonate and dried with anhydrous sodium sulfate. The crude product obtained after concentration was purified by silica gel column chromatography (20% to 50% EtOAc in hexane) and provided 5.27 g of desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.43 (br s, 9H), 4.15 (br s, 2H), 5.18 (s, 2H), 5.20 (m, 2H), 5.82 (m, 1H), 6.39 (br s, 1H), 7.36 (m, 5H). Mass spectrum: (M+H)$^+$=307.

C. N(1)-t-butyloxycarbonyl-N(2)-formylmethyl-N(2)-benzyloxycarbonyl hydrazine.

A solution of 6.5 g of the compound from Example 26B in 100 ml of methanol was cooled with a dry ice/acetone bath. Ozone was bubbled in for 1.75 h until a pale blue color persisted. Air was passed through the solution for 10 min and then 15.6 ml of dimethyl sulfide was added and the reaction mixture was allowed to warm gradually to RT overnight. Solvent was evaporated in vacuo and the residue was dissolved in ethyl acetate and washed with water, then brine several times. The organic layer was dried with anhydrous sodium sulfate, filtered and conc. in vacuo to provide 7.2 g of the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.40 (br s, 9H), 4.35 (m, 2H), 5.20 (s, 2H), 6.65 (br s, 1H), 7.36 (s, 5H), 9.70 (br s, 1H). Mass spectrum: (M+NH$_4$)$^+$=326.

D. N-[2-(N-(2)-benxyloxycarbonyl-N-(1)-t-butyloxycarbonylhydrazinyl] ethyl-L-Valine methyl ester.

To a solution of 7.2 g of the compound from Example 26C in 100 ml of methanol was added 3.55 g of L-valine methyl ester hydrochloride, followed by 3.48 g of sodium acetate and 1.33 g of sodium cyanoborohydride. The reaction mixture was stirred at RT overnight. The mixture was filtered and concentrated in vacuo. The crude product was purified by silica gel column chromatography (2% MeOH in CH$_2$Cl$_2$) to provide 5.8 g of desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.90 (d, J=6Hz, 6H), 1.43 (br s, 9H), 1.87 (m, 1H), 2.60-3.0 (m, 4H), 3.72 (s, 3H), 5.18 (s, 2H), 7.37 (m, 5H). Mass spectrum: (M+H)$^+$=424.

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E. 2S-[4-benzyloxycarbonylaza-1-tetrahydro-pyrimid-2-onyl)-3-methyl-butanoic acid methyl ester.

A solution of 2.4 g of the compound from Example 26D in 20 ml of HCl in dioxane was stirred at RT under argon for 1 h. Solvent was evaporated in vacuo and the residue was washed with satd. sodium bicarbonate and extracted with ethyl acetate. The organic layer was dried, filtered and concentrated in vacuo. The crude product was dissolved in 28 ml of CH_2Cl_2 and 0.56 g of carbonyldiimidazole was added. The solution was left at RT for 48 h. The solvent was removed and the residue was purified by silica gel column chromatography (10% to 30% EtOAc in CH_2Cl_2) to give 0.78 g of desired compound. 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J=7Hz, 3H), 0.98 (d, J=7Hz, 3H), 2.17 (m, 1H), 3.34 (m, 1H), 3.61 (m, 2H), 3.72 (s, 3H), 3.98 (m, 1H), 4.71 (d, J=10Hz, 1H), 5.20 (s, 2H), 6.72 (br s, 1H), 7.38 (m, 5H). Mass spectrum: $(M+H)^+$=350.

F. 2S-(4-Benzyloxycarbonylaza-1-tetrahydro-pyrimid-2-onyl)-3-methyl-butanoic acid.

Hydrolysis of 0.78 g of the compound from Example 26E using lithium hydroxide in aqueous dioxane provided 0.35 g of desired compound. 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.85 (d, J=7Hz, 3H), 1.04 (d, J=7Hz, 3H), 2.40 (m, 1H), 3.40 (m, 1H), 3.50 (m, 1H), 3.80 (m, 2H), 3.95 (d, J=10Hz, 1H), 5.20 (s, 2H), 7.30 (s, 1H), 7.36 (s, 5H). Mass spectrum: $(M+H)^+$=336.

G. (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5[2S-(benzyloxycarbonylaza-1-tetrahydro-pyrimid-2-onyl)-3-methyl-butanyl]amino-1,6-diphenylhexane.

Coupling of the amino compound from Example 1N with the acid from Example 26F using standard coupling procedure (EDAC/DMF) provided the desired compound (36%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.72 (d, J=7Hz, 3H), 0.83 (d, J=7Hz, 3H), 2.20 (s, 6H), 2.65 (m, 1H), 2.83 (m, 1H), 3.0-3.10 (m, 4H), 3.90 (m, 1H), 6.65 (m, 1H), 7.0-7.35 (m, 18H). Mass spectrum: $(M+H)^+$=764.

H. (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5[2S-(4-aza-1-tetrahydro-pyrimid-2-oxyl)-3-methyl-butanoyl]amino-1,6-diphenylhexane.

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Removal of the benzyloxycarbonyl protecting group of the compound from Example 26G by hydrogenolysis using 10% palladium on carbon as catalyst provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.83 (d, J=4.5Hz, 3H), 0.86 (d, J=4.5Hz, 3H), 1.80 (m, 1H), 2.20 (s, 6H), 2.58 (m, 1H), 2.67 (m, 1H), 2.90 (m, 2H), 3.0 (m, 2H), 3.80 (m, 1H), 4.20 (m, 3H), 6.72 (m, 1H), 7.0 (m, 2H), 7.20 (m, 11H). Mass spectrum: (M+H)$^+$=630.

Example 27
(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]amino-1-phenyl-6-methylheptane.

A. (2S,3S,5S)-2-Amino-3-hydroxy-5-(t-butyloxycarbonylamino)-1-phenyl-6-methylheptane.

Following the procedures described in Example 1A to Example 1F-1, but substituting isopropylmagnesium chloride for benzylmagnesium chloride in Example 1C provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.88 (d, J=7Hz, 3H), 0.92 (d, J=7Hz, 3H), 1.43 (s, 9H), 1.50-1.80 (m, 4H), 2.55 (m, 1H), 2.90 (m, 1H), 3.0 (m, 1H), 3.54 (m, 2H), 4.62 (m, 1H), 7.30 (m, 5H). Mass spectrum: (M+H)$^+$=337.

B. (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-(t-butyloxycarbonylamino)-1-phenyl-6-methylheptane.

Coupling of the amino compound from Example 27A with the acid from Example 1H using standard EDAC coupling procedure provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.85 (d, J=7Hz, 3H), 0.90 (d, J=7Hz, 3H), 1.43 (s, 9H), 1.70 (m, 2H), 2.20 (s, 6H), 3.03 (d, J=8Hz, 2H), 3.42 (m, 1H), 3.80 (m, 1H), 4.20 (m, 2H), 4.22 (s, 2H), 4.55 (m, 1H), 7.0 (m, 3H), 7.30 (m, 5H). Mass spectrum: (M+H)$^+$=499.

C. (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-amino-1-phenyl-6-methylheptane.

Removal of the t-butyloxycarbonyl protecting group of the compound from Example 27B using the procedure of Example 1N provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.90 (d, J=3Hz, 3H), 0.94 (d, J=3Hz,

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3H), 1.60 (m, 4H), 2.20 (s, 6H), 2.85 (m, 2H), 3.0 (m, 1H), 3.85 (m, 1H), 4.20 (m, 2H), 7.0 (m, 2H), 7.35 (m, 6H). Mass spectrum: (M+H)$^+$=399.

D. (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S,(1-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]amino-1-phenyl-6-methylheptane.

Coupling of the amino compound from Example 27C with the acid from Example 2A using standard coupling procedure (EDAC/DMF) provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.88 (m, 12H), 1.67 (m, 2H), 1.90 (m, 1H), 2.20 (s, 6H), 3.0 (d, J=8Hz, 2H), 3.22 (m, 4H), 3.67 (m, 1H), 3.77 (m, 1H), 4.20 (s, 2H), 4.40 (m, 1H), 4.76 (m, 1H), 7.0 (m, 3H), 7.30 (m, 5H). Mass spectrum: (M+H)$^+$=581.

Example 28
(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2,4-dionyl)-3-methylbutanoyl]amino-1-phenyl-6-methylheptane.

Coupling of the amino compound from Example 27C with the acid from Example 25D using standard coupling procedure (EDAC/DMF) provided the desired compound. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.83 (d, J=7Hz, 6H), 0.92 (t, J=7Hz, 6H), 1.73 (m, 2H), 2.18 (s, 6H), 2.30 (m, 1H), 2.62 (m, 2H), 3.03 (m, 2H), 3.45 (m, 1H), 3.55 (m, 1H), 4.72 (m, 2H), 4.20 (m, 4H), 6.40 (br d, J=9Hz, 1H), 7.0 (m, 3H), 7.30 (m, 5H), 7.62 (br s, 1H). Mass spectrum: (M+H)$^+$=595.

Example 29.
(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-piperazin-2,3-dionyl)-3-methylbutanoyl]amino-1,6-diphenylhexane.
A. 2S-(4-benzyloxycarbonyl-1-piperazin-2,3-dionyl)-3-methylbutanoic acid methyl ester.

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To a solution of 0.77 g of N-(benzyloxycarbonylamino)-ethyl-L-Valine methyl ester in 20 ml of toluene and 10 ml of acetonitrile was added 0.79 g of oxalyl diimidazole. The reaction mixture was kept at 50°C for 24 h and 0.2 g of oxalyl diimidazole was added. The reaction mixture was kept at 50°C for another 72 h. Evaporation of solvent *in vacuo* and purification of the crude product by silica gel column chromatography (10% EtOAc in CH_2Cl_2) provided the desired compound. 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.95 (d, J=7 Hz, 3H), 1.03 (d, J=7Hz, 3H), 2.20 (m, 1H), 3.60 (m, 1H), 3.73 (s, 3H), 3.85 (m, 1H), 4.0 (m, 1H), 4.10 (m, 1H), 4.90 (d, J=10 Hz, 1H), 5.36 (s, 2H), 7.20 (m, 5H). Mass spectrum: $(M+NH_4)^+$=380.

B. 2S-(1-piperazin-2,3-dionyl)-3-methylbutanoic acid methyl ester.

Removal of the benzyloxycarbonyl protecting group of the compound from Example 29A by hydrogenolysis using 10% Pd/C as catalyst provided the desired compound. 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.95 (d, J=7 Hz, 3H), 1.03 (d, J=7 Hz, 3H), 2.20 (m, 1H), 3.50 (m, 3H), 3.74 (s, 3H), 3.83 (m, 1H), 5.0 (d, J=10 Jz, 1H), 7.30 (br s, 1H). Mass spectrum: $(M+H)^+$=229.

C. (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5[2S-(1-piperazin-2,3-dionyl)-3-methylbutanoyl]amino-1,6-diphenylhexane.

The methyl ester from Example 29B was hydrolyzed using the procedure of Example 1M and the resulting acid was coupled to the amino compound from Example 1N using standard EDAC coupling procedure to provide the desired compound. 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.82 (d, J=6 Hz, 3H), 0.85 (d, J=6 Hz, 3H), 1.80 (m, 2H), 2.18 (m, 1H), 2.20 (s, 6H), 2.65 (m, 1H), 2.82-3.0 (m, 4H), 3.30 (m, 3H), 3.70 (m, 1H), 3.82 (m, 1H), 4.22 (m, 3H), 4.54 (d, J=10 Hz, 1H), 6.30 (br s, 1H), 6.65 (br d, 1H), 7.0-7.30 (m, 13H). Mass spectrum: $(M+H)^+$=643.

Example 30
(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5[2S-(4-aza-4,5-dehydro-1-pyrimid-2-onyl)-3-methyl-butanoyl]amino-1,6-diphenylhexane.

A. 2S-(4-Aza-4,5-dehydro-1-pyrimid-2-onyl)-3-methyl-butanoic acid.

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From the hydroysis product mixture of Example 26F, the desired product was isolated after column chromatography (5% MeOH/5% AcOH in CH_2Cl_2) in 12.5% yield. 300 MHz ^{1}H NMR (CD_3OD) δ 0.93 (d, J=7Hz, 3H), 1.04 (d, J=7Hz, 3H), 2.20 (m, 1H), 3.92 (dd, J=15, 3 Hz,, 1H), 4.09 (dd, J=15, 3 Hz, 1H), 4.50 (d, J=10 Hz, 1H), 6.95 (t, J=3Hz, 1H). Mass spectrum: $(M+H)^+$=334.

B. (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5[2S-(4-aza-4,5-dehydro-1-pyrimid-2-oxyl)-3-methyl-butanoyl]amino-1,6-diphenylhexane.

Coupling of the compound from Example 1N with the acid from Example 30A using standard coupling procedure (EDAC/DMF) provided the desired compound (70%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.80 (d, J=7Hz, 3H), 0.85 (d, J=7Hz, 3H), 1.75 (m, 2H), 2.15 (m, 1H), 2.20 (s, 6H), 2.62 (m, 1H), 2.85 (m, 1H), 3.02 (m, 2H), 3.55 (m, 2H), 3.80 (m, 1H), 4.20 (m, 4H), 6.38 (br d, 1H), 6.72 (t, J=3 Hz,1H), 7.0 (m, 3H), 7.22 (m, 10H), 7.63 (s, 1H). Mass spectrum: $(M+H)^+$=628.

Example 31
cis-N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-(2S-(1-tetrahydropyrimid-2-onyl)-3-methylbutanoyl)aminobutyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide

The title compound can be prepared by coupling the product of Example 2A with cis-N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-aminobutyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide (disclosed in PCT Patent Application No. WO9426749 and U.S. Patent No. 5,196,438, issued March 23, 1993, both of which are incorporated herein by reference) using a standard coupling procedure (EDAC in DMF).

Example 32
cis-N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-thiophenyl-3(S)-(2S-(1-tetrahydropyrimid-2-onyl)-3-methylbutanoyl)aminobutyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide

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The title compound can be prepared by coupling the product of Example 2A with cis-N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-thiophenyl-3(S)-aminobutyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide (disclosed in PCT Patent Application No. WO95/09843, published April 13, 1995 and U.S. Patent No. 5,484,926, issued January 16, 1996, both of which are incorporated herein by reference) using a standard coupling procedure (EDAC in DMF).

Example 33
4-Amino-N-((2syn, 3S)-2-hydroxy-4-phenyl-3-(2S-(1-tetrahydropyrimid-2-onyl)-3-methylbutanoylamino)-butyl)-N-isobutyl-benzenesulfonamide

The title compound can be prepared by coupling the product of Example 2A with 4-Amino-N-((2syn, 3S)-2-hydroxy-4-phenyl-3-amino)-butyl)-N-isobutyl-benzenesulfonamide (disclosed in PCT Patent Application No. WO94/05639, published March 17, 1994, which is incorporated herein by reference) using a standard coupling procedure (EDAC in DMF).

Example 34
A. Alternative Preparation of (2S, 3S, 5S) -2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-amino-1,6-diphenylhexane

To a 1 liter 3-necked flask equipped with a mechanical stirrer, J-Kem® temperature probe, dropping addition funnel, and dry nitrogen line was charged 30.0 g (54.87 mmol) of the product of Example 1I and 120 mL of acetonitrile. The resultant slurry was cooled to 0-5°C and 54.1 g (549 mmol) of 37% aqueous hydrochloric acid was slowly added, maintaining an internal temperature of not more than +5°C during the addition. The reaction mixture was stirred at 0-5°C and samples were taken periodically to analyze for consumption of starting material by HPLC (Zorbax C-8 column, mobile phase = 1:1 acetonitile/0.1% aqueous phosphoric acid, flow rate = 1.5 mL/minute, detection at 205 nm).

After stirring for 3 hours the reaction was complete. The reaction was quenched by the slow addition of 105 mL of 20% aqueous sodium hydroxide, again maintaining an internal temperature of not more than +5°C during the addition. Once the pH of the reaction mixture was confirmed to be basic, the

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solution was warmed to room temperature. Ethyl acetate (180 mL) was added with mixing and, after settling, the lower aqueous phase was separated and discarded. The organic phase was then washed once with 105 mL of 10% aqueous sodium chloride.

The title compound was crystallized from 12 mL/g of 1:2 ethyl acetate/heptane (yield 80-85%).

B. Alternative Preparation of (2S, 3S, 5S) -2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-amino-1,6-diphenylhexane

To a round-bottom 3-neck 1L flask with attached mechanical stirbar and thermometer was added the product of Example 1I (51.6 g, 0.095 mol) and 100 mL of glacial acetic acid. To the resulting suspension was added 35% aqueous HCl (10.5 mL, 0.103 mol) in 1 portion. The solution was allowed to stir under a N_2 atmosphere for 3h, at which time an additional 10.5 mL of 35% aqueous HCl was added. After an additional 1.5h, the reaction flask was immersed in an ice bath and a NaOH solution (16 mL, 0.198 mol) was added at a rate to maintain the internal temperature of the flask below 30 °C. Water (200 mL) was added and the mixture extracted with 4 x 200 mL of Isopropyl Acetate. The combined organic layers were washed with 2.5M NaOH (2 x 200 mL), 100 mL H_2O, brine, dried over Na_2SO_4, filtered and evaporated in vacuo to yield 39.7g (94% crude) of product as a colorless solid in greater than 95% purity by HPLC. The product could be further purified by dissolving in 200 mL isopropanol heated over a steam bath, allowed to cool with stirring to 0-5 °C to yield 32.2g (76%) of the desired product, m.p. = 131 °C.

Example 35
Alternative Preparation of 2S-(1-Tetrahydro-pyrimid-2-onyl)-3-methyl butanoic acid

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A. N-phenoxycarbonyl-L-valine

N-phenoxycarbonyl-L-valine may be prepared according to the procedures disclosed in U.S. Patent Application No. 08/08/671,893, filed June 28, 1996, which is incorporated herein by reference, and which include the following method.

Into a reactor equipped with an overhead stirrer, chiller, pH probe and thermocouple was added lithium chloride (15.6 kg, 368 moles), L-valine (26.0 kg, 222 moles), neutral alumina (8.1 kg, 150 mesh, Aldrich) and 156 kg of distilled water. The heterogeneous mixture was stirred and cooled to -14°C ± 5°C. The pH was adjusted to 10.1 with 10% aqueous lithium hydroxide. Precooled (-20°C) phenylchlorformate (36.6 kg, 234 moles) was added while maintaining a temperature of not more than -9 °C and the pH was controlled during the reaction (maintaining a pH within the range of 9.5 to 10.5 with a target of 10.0) using a continuous addition of 10% aqueous lithium hydroxide.

The reaction was stirred for 2 hours at about -14°C. The reaction mixture was filtered through Celite and the filter cake was washed with 42 kg of distilled water. The aqueous filtrate was extracted with methyl t-butyl ether (65 kg) to remove residual phenol. The aqueous phase was then cooled to 0-5°C and mixed with 200 kg of toluene. The stirred biphasic solution was adjusted to pH 1.8-2.0 with 25% (w/w) sulfuric acid. The toluene layer was concentrated at not more than 40 °C to approximately 120 L, filtered (30 kg rinse of toluene) and then concentrated again at not more than 40 °C to approximately 120 L.

To the resulting solution was added 44.2 kg of heptane and the resulting solution was heated to 40 °C ± 10°C for 15 minutes. The heat was removed and the solution was seeded and stirred overnight.· The product crystallized on the walls of the reactor and was resuspended in 80 kg of toluene, reconcentrated at not more than 50 °C to approximately 130 L, then 45.2 kg of heptane was added. The resulting solution was then heated to 40 °C ± 10°C for not less than 15 minutes and then cooled at not more than 20 °C/hour to 18 °C ± 5°C. After not less than 12 hours, the resulting white slurry was cooled to 14 °C ± 5°C and stirred for not less than 3 hours. The white slurry was filtered and the solid washed with 41 kg of 1:1 toluene/heptane. The solid

product was dried at not more than 50 °C to provide the desired product (47.8 kg) as a white powder.

B. 2S-(1-Tetrahydro-pyrimid-2-onyl)-3-methyl butanoic acid

A mixture of N-phenoxycarbonyl-L-valine (25 g, 0.106 mol) and 3-chloropropylamine hydrochloride (15.2 g, 0.116 mol) in THF (250 mL) was cooled to 2°C. Sodium hydroxide (12.7 g, 0.318 mol) was added to the stirring suspension. After about 35 minutes, a slow exotherm to 10°C occurred. The reaction was stirred at less than 10°C for 2 hours. A solution of potassium t-butoxide (29.6 g, 0.265 mol) in 125 mL of THF was added over 10 minutes, followed by a 20 mL THF rinse. The temperature of the reaction mixture was allowed to rise to 20°C during the addition. The reaction mixture was stirred at room temperature for 19 hours.

The reaction mixture was quenched with 200 mL of distilled water and then acidified to pH 9 using 26.2 g of concentrated hydrochloric acid, keeping the temperature below 30°C. The aqueous layer was separated and washed with another 125 mL of THF. Ethanol 3A (75 mL) was added to the separated aqueous layer and the mixture was acidified to pH < 3 with 12.3 g of concentrated hydrochloric acid, keeping the temperature below 25°C. The acidified mixture was extracted twice with ethyl acetate (250 mL and 150 mL). The combined organic layers were evaporated to dryness on a rotary evaporator at a temperature below 50°C. The residual solids were flushed with 250 mL of ethyl acetate. The residual solid was dissolved in 150 mL of ethanol 3A at reflux temperature and filtered through a 5 g Darco-G60 bed over filteraid, followed by a 50 mL hot ethanol rinse. The filtrate was evaporated to dryness on a rotary evaporator at a temperature below 50°C. Ethyl acetate (75 mL) was added to the residue and refluxed for 30 minutes. The suspension was cooled to below 10°C for 2 hours. The solid was collected by filtration and washed with 20 mL of cold ethyl acetate (5-8°C). After drying at 40°C for 72 hours the desired product was obtained as a white solid (15.6 g, 74%).

Example 36
Alternative Preparation of 2S-(1-Tetrahydro-pyrimid-2-onyl)-3-methyl butanoic acid

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A mixture of phenoxycarbonyl-L-valine (250 g, 1.05 mol; prepared according to the procedure disclosed in U.S. Patent Application No. 08/671,893, filed June 28, 1996, which is incorporated herein by reference) and 3-chloropropylamine hydrochloride (151 g, 1.16 mol) in THF (2.5 L) is cooled to 2°C. Sodium hydroxide (127 g, 3.2 mol) is added to the stirring suspension. After about 45 minutes, a rapid exotherm to 10°C occurrs. The reaction is stirred at 1-5°C for 2 hours. Additional 3-chloropropylamine (10 g, 0.08 mol) is added and stirring is continued for 1 hour. A solution of potassium t-butoxide (296 g, 2.6 mol) in 1.25 L of THF is then added over 30 minutes, followed by a 100 mL THF rinse. The temperature of the reaction mixture was allowed to rise to 20°C during the addition. The reaction mixture is stirred at room temperature for 12-16 hours.

The reaction mixture is quenched with 2 L of distilled water and cooled to 12°C and then acidified to pH 9 using 258 g (2.6 mol) of concentrated hydrochloric acid, keeping the temperature below 30°C. The aqueous layer is separated. Ethanol 3A (625 mL) is added to the separated aqueous layer and the mixture was acidified to pH < 3 with 116 g (1.2 mol) of concentrated hydrochloric acid, keeping the temperature below 25°C. The acidified mixture is extracted twice with ethyl acetate (2.5 L and 1.5 L). The combined organic layers are evaproated to dryness on a rotary evaporator at a temperature below 50°C. The residual solids are dried by repeated distillation with ethyl acetate (4 x 1 L). The residual solid is dissolved in 750 mL of methanol and treated with decolorizing carbon (10 g Darco-G60 bed) at room temperature overnight. The carbon is removed by filtration through diatomaceous earth. The filtrate is evaporated to dryness on a rotary evaporator at a temperature below 50°C. Ethyl acetate (1.5 L) is added to the residue and approximately 500 mL is removed on the rotary evaporator. The suspension is cooled to below 10°C for > 1 hour. The solid is collected by filtration and washed with 2 x 100 mL of cold ethyl acetate (5-8°C). After drying at 50°C for 72 hours the desired product is obtained.

Example 37

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Alternative Preparation of 2S-(1-Tetrahydro-pyrimid-2-onyl)-3-methyl butanoic acid

A. (S)-(-)-N-carboxymethyl-N(β)cyanoethyl Valine

To a 5L 3-neck round bottom flask with a mechanical stirrer was added (S)-valine (170.1g, 1.45mol) and water 145mL. The solution was cooled to 0°C with an ice-water bath and a solution of 1.0eq of KOH (93g of 88% solid KOH) in 180mL water was added dropwise over 20 minutes. After the addition was complete, acrylonitrile 1.0eq (95.5mL) was added dropwise with vigorous stirring while maintaining the internal temperature of the flask below 5°C. The solution was allowed to stir between 0-5°C for 4.5h. Water (600mL) was added and a pH meter was inserted into the solution. Methyl chloroformate 1.0eq (112mL) was added dropwise while maintaining the pH of the solution between 9.5 and 10.5, with solution of 10% aq KOH. The addition took place over 0.5h. The solution was then acidified with conc. HCl and phosphoric acid to pH 2 and was subsequently extracted with 2L of isopropyl acetate. The organic layer was concentrated under vacuum to give 201 g (60%) of a colorless oil that solidified on standing. mp 65-66°C. Optical rotation sodium D line at 25°C -0.44 (c=4.3, ethanol). IR (cm^{-1}, CDCl$_3$) 2960, 1740, 1710,1470. ^{1}H NMR (300 MHz,CDCl$_3$); (δ TMS, 0.00) ppm 0.93 (d,3H J=7Hz); 1.07 (d,3H J=6Hz); 2.16-2.36 (m,1H); 2.62-2.86 (m,2H); 3.62 (t,2H, J=7.5Hz); 3.77 (s,1.2H rotamer); 3.82 (s,1.8H rotamer); 4.15-4.30 (m,1H); 9.76-9.96 (brs,1H). ms (DCl/NH$_3$) 246, 185, 146, 125. FAB hrms: cal for (M+H$^+$): 229.1188; found: 229.1185.

B. 2S-(1-Tetrahydro-pyrimid-2-onyl)-3-methyl butanoic acid

To a 2L pressure vial was added the product of Example 37A (190g, 0.833 mol), water (900mL) and KOH (3eq, 140g). To this solution at ambient temperature was added Nickel Aluminum alloy (Raney-Type) 75g. Note that this is the unactivated form. The solution was sealed in a pressure bomb and was placed under 60 psi of hydrogen. The resulting solution was heated to 100°C for 4h. After cooling the solution to ambient temperature, it was filtered, washed with 900mL of dichloromethane and subsequently acidified to pH 1. The aqueous solution was extracted with 2 X 900mL of dichloromethane. The

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combined organic layers were concentrated to give 120g of crude product which was slurried in isopropyl acetate to give 70g of the title compound.

Example 38
Alternative Preparation of (2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane

A-1. 2S-(1-Tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl chloride
2S-(1-Tetrahydro-pyrimid-2-onyl)-3-methyl butanoic acid (17.6 g, 87.9 mmole) was slurried in THF (240 mL) and cooled to <5 °C. Thionyl chloride (14.3 g, 120 mmole) was added over 5 minutes (exothermic). The slurry was stirred at 20 °C for 70 min. until complete by HPLC (samples quenched into methanol). THF was removed by rotary evaporation; heptane (90 mL) was added and removed by rotary evaporation, yielding a wet solid mass. The material was slurried in DMF (85 mL).

A-2. Alternative Preparation of 2S-(1-Tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl chloride
2S-(1-Tetrahydro-pyrimid-2-onyl)-3-methyl butanoic acid (39.6 g, 198 mmole) was slurried in THF (590 mL) and cooled to 1 °C. Thionyl chloride (28.3 g, 238 mmole) was added over 5 minutes (exothermic). The slurry was stirred at 20 °C for 2 hours. THF was removed on the rotary evaporator; THF (200 mL) was added and removed on the rotary evaporator, yielding a wet solid mass. The material was slurried in DMF (225 mL).

B-1. (2S, 3S, 5S)-2-N,N-dibenzylamino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane
(2S, 3S, 5S)-2-N,N-dibenzylamino-3-hydroxy-5-amino-1,6-diphenylhexane (ca. 83 mmole; U.S. Patent No. 5,491,253, issued February 13,

1996, which is incorporated herein by reference) and imidazole (8.2 g, 120 mmole) were dissolved in ethyl acetate (350 mL, KF < 0.1%) and cooled to 2 °C. The slurried product of Example 38A-1 was added (exothermic, maximum temp. was 10 °C), followed by a DMF rinse (15 mL). The reaction was stirred cold initially then allowed to slowly warm to room temperature and stirred overnight.

The reaction was quenched with 100 mL water and stirred 30 minutes. The organic layer was separated and washed with 3 x 125 mL 5% NaCl. The organic solution was filtered and concentrated on rotary evaporator to a thick syrup, 62 g. HPLC purity approx. 85% (peak area). Isomer content approx. 11.2%.

CIMS (NH$_3$) m/z 647 (M + H)$^+$.

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.35-7.13 (m, 10H), 7.13-7.06 (m, 1H), 6.87 (br d, 1H), 5.22 (br s, 1H), 4.28 (d, 1H), 4.20-4.05 (m, 1H), 3.95 (d, 2H), 3.65-3.56 (m, 1 H), 3.37, (d, 2H), 3.12-2.89 (m, 5H), 2.83-2.53 (m, 4H), 2.23-2.08 (m, 1H), 1.74-1.40 (m, 4H), 0.87-0.75 (m, 6H).

^{13}C NMR (75 MHz, CDCl$_3$) δ 170.0, 156.6, 140.2, 139.1, 138.4, 129.3, 129.1, 128.9, 128.4, 128.3, 128.0, 127.1, 126.0, 125.8, 69.1, 64.0, 63.1 (br), 54.2, 49.2, 41.2, 40.5, 40.0, 39.7, 31.5, 25.4, 21.6, 19.5, 18.6.

B-2. Alternative Preparation of (2S, 3S, 5S)-2-N,N-dibenzylamino-3-hydroxy-5-
[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-
diphenylhexane

(2S, 3S, 5S)-2-N,N-dibenzylamino-3-hydroxy-5-amino-1,6-diphenylhexane (ca. 180 mmole; U.S. Patent No. 5,491,253, issued February 13, 1996, which is incorporated herein by reference) and imidazole (38.1 g, 560 mmole) were dissolved in ethyl acetate (675 mL, KF < 0.1%) and cooled to 1 °C. The slurried product of Example 38A-2 was added slowly over 30 minutes (exothermic, maximum temp. was 6 °C), followed by an ethyl acetate rinse (225 mL). The reaction was stirred cold for 1. 5 hours, then allowed to slowly warm to about 27°C and stirred for about 20 hours.

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The reaction was quenched with a dilute solution of HCl (36.75 g concentrated HCl in 225 mL of water) and stirred 20 minutes. The biphasic mixture was filtered with a 100 mL ethyl acetate rinse. The organic layer was separated and washed with 3 x 125 mL 5% NaCl. The organic layer was separated and washed with 3 x 225 mL 5% NaCl and 2 x 225 mL 5% NaHCO$_3$. The organic solution was concentrated by rotary evaporation to provide the desired product as a thick syrup.

C. (2S, 3S, 5S)-2-Amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane

The crude product of Example 38B (ca. 83 mmole) was dissolved in methanol (260 mL). Pd/C (50% wet Pearleman's catalyst, 10.4 g wet weight) and ammonium formate (15.1 g, 239 mmole) were added and the mixture was warmed to 50 °C. After 2.5 hours the reaction was complete by TLC. The mixture was cooled to 35 °C and catalyst was removed by filtration through diatomaceous earth, followed by a methanol rinse (250 mL). The combined filtrate was concentrated on the rotary evaporator. The residue was dissolved in dioxane (150 mL) with warming. Dioxane was removed on the rotary evaporator to yield 60 g of yellow oil. HPLC purity approx. 88.2% (peak area). Isomer content ≥7.9% (however, one isomer does not separate from the main peak).

CIMS (NH$_3$) m/z 467 (M + H)$^+$

^{1}H NMR (300 MHz, CD$_3$OD) δ 7.35-7.10 (m, 10H), 4.40-4.20 (m, 1H), 4.25 (d, 1H), 3.68-3.57 (m, 1H), 3.20-3.09 (m, 2H), 3.08-2.90 (m, 3H), 2.90-2.74 (m, 2H), 2.65-2.49 (m, 2H), 2.20-2.04 (m, 1H), 1.92-1.78 (m, 1H), 1.78-1.60 (m, 2H), 1.60-1.45 (m, 1H), 0.88-0.77 (m, 6H)

^{13}C NMR (75 MHz, CD$_3$OD) δ 171.3, 158.4, 140.5, 139.8, 130.6, 130.4, 129.5, 129.3, 127.3, 127.0, 71.5, 63.9, 57.1, 49.1, 41.8, 41.6, 41.4, 40.7, 40.5, 26.9, 22.5, 20.0, 18.9

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.35-7.13 (m, 10H), 5.35 (s, 1H), 4.40-4.23 (m, 2H), 3.60-3.52 (m, 1 H), 3.25-2.65 (m, 8H), 2.58-2.45 (dd, 1H), 2.30-2.10 (m, 1H), 1.90-1.65 (m, 3H), 1.65-1.50 (m, 1H), 0. 91 (d, 3H), 0.84 (d, 3H)

^{13}C NMR (75 MHz, CDCl$_3$) δ 171.2, 156.6, 139.1, 138.5, 129.3, 129.2, 128.5, 128.2, 126.3, 126.0, 71.6, 63.1 (br), 56.3, 48.7, 41.6, 41.0, 40.6, 40.0, 39.6, 25.5, 21.7, 19.7, 18.7

D.   (2S, 3S, 5S)-2-Amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane   (S)-Pyroglutamic acid salt

The crude product of Example 38C was dissolved in dioxane (370 mL, KF = 0.07% moisture). S-Pyroglutamic acid (10.3 g, 80 mmole) was added and the suspension was warmed to 50 °C to give a clear solution. After stirring 1 hour the solution was seeded with a few crystals of the product salt. The salt slowly precipitated. The slurry was slowly cooled and stirred overnight at room temperature. The product was isolated by filtration and washed with dioxane (100 mL). Wet cake weight was 120 g. Product was dried at 60 °C in a vacuum oven with nitrogen purge. Yield 35.2 g off-white powder. HPLC purity: >98% (peak area including pyroglutamic acid). Isomer content approx. 1% (however, one isomer does not separate from the main peak).

mp = 135-141 °C

$[a]_D^{25}$ = -21.9° (c=2.5, CH$_3$OH)

CIMS (NH$_3$) m/z 467 (M + H for base)[+], 147 (M + NH$_4$ for pyroglutamic acid)[+], 130 (M + H for pyroglutamic acid)[+]

IR (KBr) 1586, 1655, 1682 cm^{-1}

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.62 (s, 1H), 7.54 (d, 1H), 7.32-7.06 (m, 10 H), 6.33 (s, 1H), 4.26 (d, 1H), 4.11-3.99 (m, 1H), 3.82 (dd, 1H), 3.57-3.48 (m, 1H), 3.27-3.19 (m, 1H), 3.08-2.95 (m, 2H), 2.92-2.70 (m, 5H), 2.53-2.43 (m, 1H),

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2.26-2.14 (m, 1H), 2.13-1.99 (m, 2H), 1.99-1.87 (m, 2H), 1.72-1.61 (m, 2H), 1.61-1.49 (m, 1H), 1.46-1.35 (m, 1H), 0.70 (d, 3H), 0.64 (d, 3H).

^{13}C NMR (100 MHz, DMSO-d$_6$) δ 176.9, 176.1, 169.2, 155.5, 138.8, 137.7, 129.3, 129.3, 128.3, 127.8, 126.4, 125.5, 66.9, 61.5, 56.9, 55.3, 46.8, 40.2, 39.6, 39.4, 38.8, 37.4, 29.8, 25.4, 25.3, 21.6, 19.6, 18.7.

^{1}H NMR (300 MHz, CD$_3$OD) δ 7.32-7.03 (m, 10H), 4.23-4.12 (m, 1H), 4.12 (d, 1H), 3.98 (dd, 1 H), 3.71-3.63 (m, 1H), 3.46-3.37 (m, 1H), 3.11-2.98 (m, 2H), 2.97-2.80 (m, 4H), 2.70-2.59 (m, 1H), 2.49-2.38 (m, 1H), 2.38-2.12 (m, 3H), 2.07-1.92 (m, 2H), 1.75-1.63 (m, 2H), 1.63-1.50 (m, 1H), 1.45-1.32 (m, 1H), 0.74-0.65 (m, 6H).

^{13}C NMR (75 MHz, CD$_3$OD) δ 181.0, 179.6, 171.6, 158.4, 139.5, 137.3, 130.5, 130.0, 129.4, 128.3, 127.2, 68.1, 64.0, 59.6, 57.7, 48.8, 41.7, 41.1, 40.7, 40.6, 37.9, 31.1, 26.9, 26.9, 22.5, 20.1, 18.9.

^{1}H NMR (300 MHz, D$_2$O) δ 7.30-6.97 (m, 10H), 4.16-4.03 (m, 1H), 3.99-3.91 (m, 2H), 3.71-3.63 (m, 1H), 3.43-3.35 (m, 1H), 3.00-2.68 (m, 6H), 2.40-2.13 (m, 5H), 1.88-1.72 (m, 3H), 1.68-1.56 (m, 1H), 1.52-1.37 (m, 1H), 1.32-1.18 (m, 1H), 0.60-0.52 (m, 6H).

^{13}C NMR (75 MHz, D$_2$O) δ 181.6, 180.1, 171.0, 157.3, 137.9, 135.2, 129.3, 129.2, 129.1, 128.4, 127.6, 126.4, 67.3, 62.6, 58.2, 56.7, 47.5, 40.1, 39.4, 39.2, 38.7, 35.7, 29.6, 25.3, 25.2, 20.5, 18.5, 17.6.

E.   (2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane
The product of Example 1H (7.26 g, 40.3 mmole) was slurried in ethyl acetate (22 mL) and thionyl chloride (5.75 g, 48.3 mmole) was added, followed

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by 1 drop DMF. The mixture was warmed to 50 °C and stirred 5 hours. The solution of the resulting acid chloride was cooled to 22 °C and held for the subsequent coupling reaction.

The product of Example 38D (20 g, 31.7 mmole, corrected for dioxane content), sodium bicarbonate (16.5 g, 197 mmole), ethyl acetate (150 mL) and water (150 mL) were combined in a flask and stirred until the product of Example 38D had dissolved (some salt remains undissolved). The solution of acid chloride prepared above was added over 5 minutes, followed by an ethyl acetate rinse (5 mL). Addition was mildly exothermic (maximum temperature 23 °C). The mixture was stirred overnight.

The organic layer was separated and washed with 5% sodium bicarbonate (100 mL) and water (100 mL). Solvent was removed on the rotary evaporator. The residue was dissolved in ethyl acetate (100 mL) and filtered, rinsing with ethyl acetate (50 mL). The solvent was removed from the combined filtrate on the rotary evaporator. The residue was dissolved in hot ethyl acetate (105 mL) and heptane (105 mL) was added; product began to crystallize rapidly. The slurry was cooled and stirred at 20-23 °C for 5 hours. Product was collected by filtration and washed with 1/1 (v/v) ethyl acetate/heptane (30 mL). Product was dried under vacuum oven at 70 °C to provide 18.8 g of the desired product as a white powder.

Example 39
Preparation of Amorphous (2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane

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A. The product of Example 38E (2.5 g) was dissolved in 8 mL of absolute ethanol. This solution was added slowly dropwise to 250 mL of chilled water at 9°C with vigorous stirring. A white solid immediately appeared. The stirring was continued for 15 minutes and the solids were collected by filtration. Vacuum drying at 50°C for 12 hours provided 2.32 g of the desired product as an amorphous solid.

B. The product of Example 38E (2.5 g) was dissolved in 6 mL of absolute ethanol. This solution was added slowly dropwise to 31 mL of chilled water at 7-9°C with vigorous stirring. A white solid appeared. The stirring was continued for 20 minutes and the solids were collected by filtration. Vacuum drying at 50°C for 12 hours provided 2.24 g of the desired product as an amorphous solid.

C. The product of Example 38E (0.5 g) was dissolved in 8 mL of isopropanol. This solution was added slowly dropwise to 100 mL of chilled water at 10-15°C with vigorous stirring. A white solid appeared. The stirring was continued for 20 minutes and the solids were collected by filtration. Air drying provided 0.48 g of the desired product as an amorphous solid.

D. The product of Example 38E (0.5 g) was dissolved in 8 mL of acetone and 0.2 mL of absolute ethanol. This solution was added slowly dropwise to 100 mL of chilled water at 10-15°C with vigorous stirring. A white solid appeared. The stirring was continued for 10 minutes and the solids were collected by filtration. Air drying provided 0.46 g of the desired product as an amorphous solid.

E. The product of Example 38E (0.5 g) was dissolved in 2 mL of acetonitrile. This solution was added slowly dropwise to 100 mL of chilled water at 10-15°C with vigorous stirring. A white solid appeared. The stirring was continued for 20 minutes and the solids were collected by filtration. Air drying provided 0.46 g of the desired product as an amorphous solid.

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Example 40
N-(3-Chloropropylaminocarbonyl)-valine methyl ester

3-Chloropropylisocyanate (0.31 mL, 3.0 mmol) was added to a slurry of L-valine methyl ester hydrochloride (0.5 g, 3.0 mmol) and triethylamine (0.42 mL, 3.0 mmol) in THF (10 mL). The reaction mixture was stirred for 4 hours at room temperature and was then quenched with the addition of aqueous sodium bicarbonate. The quenched reaction mixture was extracted with ethyl acetate. The organic layer was separated, dried and evaporated to give the desired product.

Example 41
(2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-4-hydroxy-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane

Reaction of a solution of the product of Example 25E in methylene chloride with sodium borohydride provides the desired product.

Example 42
(2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-6-hydroxy-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane

A 300-mL incubation of (2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-6-hydroxy-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane labelled with ^{14}C in the carbonyl group of the acetyl moiety (50 μM, 6.0 μCi) was performed with rat liver microsomes (0.5 mg/mL microsomal protein) and an NADPH-generating system for 60 minutes at 37°C. The metabolic reaction was stopped by adding 300 mL of acetonitrile. The supernatant obtained after centrifugation at 3000 RPM for 10 minutes was evaporated to dryness *in vacuo*. The residue was reconstituted in 2 mL of HPLC mobile phase. Isolation of the desired product was achieved at ambient temperature with a Beckman Ultrasphere 5 μm 10 x 150 mm C_{18} column connected to an Alltech Ultrasphere 5 μm C_{18} cartridge guard column. A linear gradient of 25-55% acetonitrile in buffer (25 mM ammonium acetate, pH

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adjusted to 4.8 with formic acid) over 57 minutes was used as column eluent at a flow rate of 2.8 mL/minute.

Fluorogenic Assay for Screening Inhibitors of HIV Protease

The inhibitory potency of the compound of the invention can be determined by the following method.

The compound of the invention is dissolved in DMSO and a small aliquot further diluted with DMSO to 100 times the final concentration desired for testing. The reaction is carried out in a 6 X 50 mm tube in a total volume of 300 microliters. The final concentrations of the components in the reaction buffer are: 125 mM sodium acetate, 1 M sodium chloride, 5 mM dithiothreitol, 0.5 mg/ml bovine serum albumin, 1.3 μM fluorogenic substrate, 2% (v/v) dimethylsulfoxide, pH 4.5. After addition of inhibitor, the reaction mixture is placed in the fluorometer cell holder and incubated at 30°C for several minutes. The reaction is initiated by the addition of a small aliquot of cold HIV protease. The fluorescence intensity (excitation 340 nM, emmision 490 nM) is recorded as a function of time. The reaction rate is determined for the first six to eight minutes. The observed rate is directly proportional to the moles of substrate cleaved per unit time. The percent inhibition is 100 X (1 - (rate in presence of inhibitor)/(rate in absence of inhibitor)).

Fluorogenic substrate: Dabcyl-Gaba-Ser-Gln-Asn-Tyr-Pro-Ile-Val-Gln-EDANS wherein DABCYL = 4-(4-dimethylamino-phenyl)azobenzoic acid, Gaba = γ-aminobutyric acid, and EDANS = 5-((2-aminoethyl)amino)-naphthalene-1-sulfonic acid.

Table 1

Compound of Example	Percent Inhibition	Inhibitor Concentration (nanomolar)
1P	92.6	0.5

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2B	93.2	0.5
3C	86.9	0.5
4F	49.7	0.5
5	80.8	0.5
6F	61.4	0.5
7B	67.1	0.5
8	55.6	0.5
9B	62.6	0.5
10F	81.0	0.5
11B	91.1	0.5
12B	76.8	0.5
13B	56.2	1.0
14D	52.7	0.5
15	48	0.5
17C	87.2	0.5
18C	57.8	0.5
19E	68.5	0.5
22E	71.8	0.5
23C	86.0	0.5
25E	100	0.5
26H	94.6	0.5
27D	92.9	0.5
28	86.6	0.5
29C	72.6	0.5
30B	91.0	0.5

Antiviral Activity

The anti-HIV activity of the compound of the invention can be determined in MT4 cells according to the following procedure. MT4 cells were infected with cell-free supernatant of HIVIIIB (previously frozen with known 50% tissue culture infectious dose ($TCID_{50}$) at 0.003 multiplicity of infection (MOI) for one hour. After one hour infection, cells were washed twice to remove residual

viruses, resuspended in culture media and seeded into 96-well tissue culture plates at 1x10^4 cells per well with various half-log dilutions of compounds. Uninfected cells are included as toxicity and cell controls. RPMI 1640 media (Gibco) with 10% fetal bovine serum were used as culture media. Various concentrations of human serum (Sigma) 50%, 25% and 12.5% were added to culture media resulting in final concentration of 60%, 35% and 22.5% total serum. All assay plates were incubated in 37 deg. cent. incubator for 5 days. MTT (sigma, 5 mg/ml stock in PBS) was added to all wells at 25 ul per well, incubate for 4 hours. 20%SDS with 0.02 N HCl in water was added at 50 ul per well to lyse cellls. Plates incubated overnight for complete lyses were read on a microtitre plate reader at 570/650 nm wavelengths to determine cell optical density (O.D.). Raw data were analysed for percent inhibition by the following formula:

$$\frac{O.D. \text{ test well} - O.D. \text{ virus control}}{O.D. \text{ cell control} - O.D. \text{ virus control}} \times 100$$

The 50% effective concentration (EC_{50}) was calculated by the median effect equation (Chou, 1975,Proc. Int. Cong. Pharmacol. 6th p. 619) to determine the efficacy of compound. The 50% lethal concentration (LC_{50}) was calculated using uninfected MT4 cells.

Under these conditions, the following data were obtained (n = 4 duplicate determinations:

Table 2

Compound of Example	IC_{50} (μM, 0% plasma)	LC_{50} (μM)

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1P	0.01	41.32
2B	0.016	17.78
3C	0.025	49.5
4F	0.101	>100
5	0.368	>100
6F	0.193	>100
7B	0.204	>100
8	0.019	17.78
9B	0.272	19.33
10F	0.047	91.97
11B	0.19	18.16
12B	0.093	19.11
14D	0.053	>100
15	0.119	>100
17C	0.051	18.96
18C	0.329	19.1
19E	0.395	17.95
20D	0.283	24.08
25E	0.012	22.88
26H	0.015	33.0
27D	0.03	56.23
28	0.011	72.2
29C	0.427	56
30B	0.003	18

In vitro generation and Characterization of HIV Resistant to the Compound of Example 2B

A. Selection for the Compound of Example 2B Resistant HIV-1 by In Vitro Passage

MT4 cells were infected with the wild-type HIV clone pNL4-3, and the virus was serially passaged in the presentce of increasing concentrations of the compound of Example 2B to select for the compound of Example 2B resistant virus strains. Virus was initially grown in the presence of 0.02 µM the compound of Example 2B (passage P1), and during the course of the five month selection procedure, the concentration of the compound of Example 2B was increased to 3.0 µM (Passage P17). While it took more than 110 days in culture to increase the drug concentration from 0.02 µM to 0.80 µM, the drug concentration could be rapidly escalated from 0.80 µM to 3.0 µM during the subsequent six weeks. The results of these selection studies are shown in Table 3 below.

Table 3. *In vitro* Selection and Phenotypic Susceptibility of Passaged HIV-1 to the compound of Example 2B

Virus	Conc. of the compound of Example 2B used in selection (µM)	No. of Days in Culture	The compound of Example 2B EC_{50} (µM)
NL4-3	NA	NA	0.028
P1	0.02	8	ND
P2	0.02	16	0.025
P3	0.04	26	ND
P4	0.04	37	0.032
P5	0.06	44	0.140
P6	0.12	58	0.149
P7	0.15	65	0.201
P8	0.21	75	0.295
P9	0.30	82	0.333
P10	0.30	93	0.464
P11	0.42	100	0.346
P12	0.62	107	0.291
P13	0.80	114	1.001
P14	1.10	121	1.115
P15	1.50	128	1.337
P16	2.00	135	1.426
P17	3.00	156	ND

B. Sequence Analysis of the HIV Protease Coding Region from Selected Passages.

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Proviral DNA sequences from infected cells from passages P4, P6, P7, and P11-P17 were cloned and sequenced. A compilation of the seven common substitutions observed during drug selection and their frequency in each passage is shown in Table 4 below.

Table 4. Frequency of Common Mutations Observed During *in vitro* Selection with the Compound of Example 2B

Passage	[inhibitor] (µM)	Frequency (No. of Clones)						
		I84V	L10F	M461	T91S	V321	I47V	I47A
4	0.04	0/3	0/3	0/3	0/3	0/3	0/3	0/3
6	0.12	6/7	2/7	0/7	0/7	2/7	0/7	0/7
7	0.15	6/6	6/6	2/6	0/6	0/6	0/6	0/6
11	0.42	7/7	7/7	7/7	5/7	0/7	0/7	0/7
12	0.62	7/7	7/7	7/7	6/7	0/7	0/7	0/7
13	0.80	5/5	5/5	5/5	3/5	1/5	1/5	0/5
14	1.10	5/5	5/5	5/5	4/5	4/5	4/5	0/5
15	1.50	5/5	5/5	5/5	5/5	4/5	4/5	0/5
16	2.00	10/10	10/10	10/10	8/10	9/10	8/10	0/10
17	3.00	5/5	5/5	5/5	4/5	0/5	0/5	5/5

For each passage except passage 4 (P4), beween five and ten individual clones were sequenced. The wild-type protease gene sequence was present in two of the three P4 clones, but was not observed in any other passage after P4.

By passage 6 (P6), a predominant I84V mutation had emerged which was present in six of seven clones. This mutation was present in every clone sequenced after P6, suggesting that it is a critical mutation selected at an early stage necessary to confer resistance to the compound of Example 2B. Analysis of the subsequent passage P7 revealed a second mutation L10F which was present in all six clones, as well as a third mutation M461 present in two of six clones. Both of these additional mutations were also maintained in all clones sequenced after passage P7, suggesting that they too, are critical in maintaning the compound of Example 2B resistance phenotype. The M461 substitution has previously been observed during selection with HIV protease inhibitors,

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and may serve to compensate for other changes present at either residue 82 or 84.

By passage P11, the emergence of a fourth highly conserved mutation T91S was observed in five of seven clones. Although clones from subsequent passages were obtained that did not contain this substitution, the T91S mutation was observed at a frequency of at least 60% in all subsequent passages. Passages P13-P16 were marked by the appearance of two additional mutation V32I and I47V. Although only present in one of five clones from passage P13, both mutations were present at a frequency of 80% in the next three passages, almost always appearing together in the same clone. Interestingly, the V32I mutation appeared in two of six clones in passage P6, , but was not observed in any other clone until passage P13. Furthermore, none of the five clones sequenced from passage P17 contained the V32I mutation. Since the V32I mutation was almost always associated with the I47V mutation in the same clone, the disappearance of the V32I mutation in passage P17 may be explained at least in part by the emergence of a second mutation at residue 47 from Val to Ala, a substitution which was present in all five clones from passage P17.

C. Susceptibility of the Passages Viruses to the Compound of Example 2B

Following the selection, viral stocks from each passage were titered, and their phenotypic resistance to the compound of Example 2B was determined using the MTT colorimetric assay. Based on this analysis, the phenotype of the passaged virus to the compound of Example 2B fell within 3 broad classes: low resistance (passages P1-P4, similar susceptibility as that of the parental pNL4-3 strain), intermediate resistance (passages P5-P12, 5 to 16-fold higher EC_{50} than pNL4-3), and high resistance (passages P13-P17, $\geq$35-fold higher EC_{50} than NL4-3).

D. Cross Resistance of the Passaged Viruses to Other Protease Inhibitors

The phenotypic susceptibility of four passaged viral strains (P7, P11, P14, and P17) to the compound of Example 2B, ritonavir, indinavir and

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saquinavir were examined. EC_{50} values are provided below in Table 5. As high-level resistance to the compound of Example 2B emerged (P14, P17), significant (18-20-fold) cross-resistance to ritonavir became evident. The P17 virus was also significantly resistant to indinavir (20-fold). However, all of the passaged virus retained substantial sensitivity ($\leq$ 4-fold change in EC_{50}) to saquinavir.

Table 5. Cross-Resistance of HIV Selected *In Vitro* by the Compound of Example 2B to Ritonavir, Indinavir and Saquinavir.

Virus	EC_{50} (μM) Compound of Example 2B	Ritonavir	Indinavir	Saquinavir
NL4-3	0.028	0.098	0.067	0.020
P7	0.116	0.221	0.113	0.033
P11	0.349	0.478	0.153	0.058
P14	1.278	1.738	0.425	0.048
P17	9.475	2.094	1.361	0.082

Additional studies were performed to compare the inhibitory activity of the compound of Example 2B against ritonavir-resistant mutant HIV clones. EC_{50} values for both compound 2B and ritonavir in the presence (50%) and absence (0%) of human serum are provided below in Table 6.

Table 6. Activity of the Compound of Example 2B Against Ritonavir-Resistant Mutant HIV Clones

% Human Serum	EC$_{50}$ (nM)			
	Compound of Example 2B		Ritonavir	
	0%	50%	0%	50%
Virus Clone				
Wild Type (pNL4-3)	22	126	71	1400
V82A	33	268	144	4080
V82F	26	147	146	3600
V82T	31	147	146	5640
V82S	26	314	304	9220
I84V	20	170	141	2720
G48V	8	156	111	1710
L90M	16	180	93	2280
I54V, V82T	213	1150	613	16,700
Wild Type (HXB2)	12	51	64	1050
E35D, M36I, I54V, A71V, V82T	83	691	1170	21,900
K20R, E35D, M36I, I54V, A71V, V82T	93	376	1420	16,000

The data show that despite the development of profound resistance to ritonavir, the compound of Example 2B is still effective against those ritonavir-resistant mutant clones.

Still additional studies were performed to test the activity of the compound of Example 2B against ritonavir-resistant HIV from patients. EC$_{50}$ values for the compound of Example 2B and ritonavir in those patients are provided below in Table 7.

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Table 7. Activity of the Compound of Example 2B Against Ritonavir-Resistant HIV from Patients

Patient No.	Day	Resistance Mutation in Sequence	EC$_{50}$ (nM)	
			Compound of Example 2B	Ritonavir
104	-1	baseline	8	21
104	21	V82A	9	46
104	28	V82T	13	67
129	-1	baseline	5	24
129	84	M36I, I54V, A71V, V82T	33	203
129	140	K20K/R, M36M/I, I54V, A71A/V, V82T	29	677
131	-28	baseline	4	18
131	88	M36I, I54V>I, V82A	15	163
131	200	K20K/R, M36I, I54I/V, V82A	52	731
224	-6	baseline	6	29
224	110	L33L/F, V82T/S	12	79
224	190	K20K/N/R, L33L/F, M36M/I, I54V/M, V82S	52	496
235	-1	baseline	6	10
235	167	I54I/V, A71V, V82A. L90L/M	6	66
313	1	baseline	4	12
313	57	M36M/I, V82F	11	64
313	85	M36M/I, I54I/V, V82S/F/A/T	25	274
410	1	baseline	6	29
410	57	M36M/I, I54I/V, V82A	33	341
410	85	M36I, I54V, V82A	97	545

The data in Table 7 show very clearly the development of resistance to ritonavir in patients. In marked contrast, however, the compound of Example 2B remains efficacious in inhibiting HIV protease in those same patients.

In summary, the above data clearly demonstrates that the use of a compound of the present invention elicits a different profile of HIV protease mutations, and, therefore a different profile of the development of resistance. In addition, the data shows that a compound of the present invention can be used to effectively inhibit HIV protease activity in patients that have already

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developed resistance to one or more other protease inhibitors which promote an HIV protease mutation pattern of the type promoted by ritonavir. The data demonstrate the value of using a compound of the invention in combination with ritonavir or an HIV protease inhibitor which promotes an HIV protease mutation pattern of the type promoted by ritonavir.

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate (isethionate), lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as loweralkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Other salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases.

Preferred salts of the compounds of the invention include hydrochloride, methanesulfonate, sulfonate, phosphonate and isethionate.

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The compounds of the present invention can also be used in the form of esters. Examples of such esters include compounds wherein a hydroxyl group in the compound of this invention has been acylated with an N-protected or unprotected amino acid residue, a phosphate function, a hemisuccinate residue, an acyl residue of the formula $R^*C(O)$- or $R^*C(S)$- wherein R^* is hydrogen, loweralkyl, haloalkyl, alkoxy, thioalkoxy, alkoxyalkyl, thioalkoxyalkyl or haloalkoxy, or an acyl residue of the formula R_a-$C(R_b)(R_d)$-$C(O)$- or R_a-$C(R_b)(R_d)$-$C(S)$- wherein R_b and R_d are independently selected from hydrogen or loweralkyl and R_a is -$N(R_e)(R_f)$, OR_e or -SR_e wherein R_e and R_f are independently selected from hydrogen, loweralkyl and haloalkyl, or an amino-acyl residue of the formula $R_{180}NH(CH_2)_2NHCH_2C(O)$- or $R_{180}NH(CH_2)_2OCH_2C(O)$- wherein R_{180} is hydrogen, loweralkyl, arylalkyl, cycloalkylalkyl, alkanoyl, benzoyl or an α-amino acyl group. The amino acid esters of particular interest are glycine and lysine; however, other amino acid residues can also be used, including those wherein the amino acyl group is -$C(O)CH_2NR_{200}R_{201}$ wherein R_{200} and R_{201} are independently selected from hydrogen and loweralkyl or the group -$NR_{200}R_{201}$ forms a nitrogen containing heterocyclic ring. These esters serve as pro-drugs of the compound of the present invention and serve to increase the solubility of these substances in the gastrointestinal tract. These esters also serve to increase solubility for intravenous administration of the compound. Other prodrugs include compounds wherein a hydroxyl group in the compound of this invention is functionalized with a substituent of the formula -$CH(R_g)OC(O)R_{181}$ or -$CH(R_g)OC(S)R_{181}$ wherein R_{181} is loweralkyl, haloalkyl, alkoxy, thioalkoxy or haloalkoxy and R_g is hydrogen, loweralkyl, haloalkyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl or dialkylaminocarbonyl. Such prodrugs can be prepared according to the procedure of Schreiber (Tetrahedron Lett. **1983**, *24*, 2363) by ozonolysis of the corresponding methallyl ether in methanol followed by treatment with acetic anhydride.

The prodrugs of this invention are metabolized *in vivo* to provide the compound of this invention . The preparation of the prodrug esters is carried out by reacting the compound of the invention with an activated amino acyl, phosphoryl, hemisuccinyl or acyl derivative as defined above. The resulting

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product is then deprotected to provide the desired pro-drug ester. Prodrugs of the invention can also be prepared by alkylation of the hydroxyl group with (haloalkyl)esters, transacetalization with bis-(alkanoyl)acetals or condensation of the hydroxyl group with an activated aldehyde followed by acylation of the intermediate hemiacetal.

Means for determining the spatial orientation of a compound of this invention are well known in the art. One preferred method is determination of the HIV protease/inhibitor complex by the technique of X-ray crystallography. - The process of determining the structures of protein/inhibitor complexes using the X-ray technique is well known (See T. L. Blundel and L. N. Johnson, Protein Crystallography, Academic Press, (1976) and Methods in Enzymology, volumes 114 and 115, H. W. Wyckoff et al., eds., Academic Press (1985)). This technique can employ, for instance, a highly purified preparation of HIV protease complexed with an inhibitor of interest in a buffered solution (typically at a pH of between about 4.5 and about 8.0). The complex is allowed to crystallize in the presence of a precipitation agent (such as ammonium sulfate) under conditions which yield single crystals of the complex. Specific conditions for crystallizing HIV protease with various inhibitors have been well documented (see, e.g., K. Appelt, Perspectives in Drug Discovery and Designs, 1, 23-48 (1993)). Application of a concentrated X-ray beam (from rotating anode X-ray generator or synchrotron) to an appropriately prepared and mounted crystal will yield a diffraction pattern from the reflected X-ray beam. Detection of the diffracted rays may be carried out by using a multiwire area detector (such as that manufactured by Siemmens Analytical X-ray Instruments, Inc. (Madison, WI)() or an R-axis II image plate system from Rigaku Corporation, The Woodlands, TX). Refinement of the X-ray diffraction data using computer software such as X-PLOR (A. T. Brunger, X-PLOR, Version 3.1: Yale University Press: New Haven, CT, 1992, distributed by Molecular Simulations, Inc.) will yield a three dimensional structure. In general, the above technique will yield a structure which may be refined to about 2 to 3 Å with an R-value of about 0.25 or less. As the skilled artisan can appreciate, these values are adequate to determine the interactions between HIV protease and a given compound such that it will be clear if the claimed features are present. Visualization of the

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complex of HIV protease and an inhibitor may be carried out using computer software such as InsightII (Biosym/Molecular Simulations, INC., San Diego) or Quanta (Molecular Simulations, Inc., Burlington MA), and distances and spherical volumes may be generated using tools available within those programs.

A second means for determining spatial orientation is the technique of Nuclear Magnetic Resonance (NMR) Spectroscopy. The process of determining the structures of protein/inhibitor complexes using the NMR technique is well known (See K. Wuthrich, NMR of Proteins and Nucleic Acids, John Wiley, (1986)). This technique can employ, for instance, a preparation of HIV protease complexed with an inhibitor of interest in a buffered solution (typically at a pH of between about 3.0 and about 8.0). Either single or multi-dimensional techniques may be applied. Advantageously, the enzyme and/or the inhibitor may be enriched with stable isotopes such as ^{13}C, ^{15}N, or ^{2}H to more easily determine the binding conformation and proximity. Specific conditions for determining the 3D structure of an inhibitor bound to HIV protease have been described in T. Yamazaki et al., Protein Science, 5, 495-506 (1996). In general, the NMR technique will yield a structure which has no distance violation greater than about 0.3 Å and an RMS deviation between the family of structures generated from the average structure of about 0.6 Å. As the skilled artisan can appreciate, these values are adequate to determine the interactions between HIV protease and a given compound such that it will be clear if the claimed features are present. Visualization of the complex of HIV protease and an inhibitor may be carried out using computer software such as InsightII (Biosym/Molecular Simulations, Inc., San Diego) or Quanta (Molecular Simulations, Inc., Burlington, MA), and distances and spherical volumes may be generated using tools available within those programs.

A third means is Molecular Modeling. This process of creating theoretical models of protein-inhibitor complexes is well known (see G. L. Seibel and P. A. Kollman, "Molecular Mechanics and the Modeling of Drug Structures, Ch. 18.2 in Comprehensive Medicinal Chemistry, C. Hansch, Ed., Pergammon Press, (1990) and T. J. Perun and C. L. Propst, Eds. Computer-

Aided Drug Design, Marcel Dekker, Inc. (1989)). Computer software such as Insight II (Biosym/Molecular Simulations, Inc., San Diego) or Quanta (Molecular Simulations, Inc., Burlington, MA) is used to construct a possible 3D arrangement of inhibitor and protein. Typically, coordinates for the protein are derived from prior X-ray or NMR structures taken from the Protein Data Base (Brookhaven National Laboratories, New York). Coordinates for the inhibitor are adopted which use standard bond lengths and angles derived from structures of organic compounds (for example, data found within the Cambridge Crystallographic Database (University Chemical Laboratory, Cambridge, United Kingdom). The candidate inhibitor is aligned in 3-dimensional space with other, related inhibitors whose bound conformations have previously been determined by either X-ray crystallography or NMR spectroscopy. Both Van der Waals volume and electrostatic potentials are used to direct the alignment process. Typically, the protein and inhibitor molecules are allowed to achieve conformations that are lower in energy from the initial starting geometry by energy minimization in which a force field is used to mathematically search for the lowest energy conformation. Suitable force fields such as AMBER (S. J. Weiner et al., Journal of Computational Chemistry, 7, 230-252 (1986) or CVFF (J. R. Maple et al., Journal of Computational Chemistry 15:162-182 (1994)) are available within the software listed above. Typically, energy minimization of the inhibitor is initially carried out with the enzyme atoms held fixed in space followed by more extensive energy minimization of the entire protein/inhibitor complex. Conformational searching (torsion driver, rotor library, or dynamics/Monte Carlo methods are available within the software listed above) is carried out to explore additional or alternative binding modes of the inhibitor within the active site of HIV protease. Water molecules may be added during this analysis to more closely simulate the aqueous environment. Usually, only one or a small number of possible inhibitor conformations remain after this entire modeling process. The accuracy of these theoretical models is frequently comparable to the accuracy of structures determined by X-ray or NMR methods, particularly when the candidate inhibitor compound is closely related to the previously studied inhibitor compounds. A specific example of the use of theoretical molecular modeling methods in the successful prediction of an HIV protease/inhibitor

complex is found in H. L. Sham et al., Journal of Medicinal Chemistry, 39:392-397 (1996). Visualization of the complex of HIV protease and an inhibitor may be carried out using computer software such as Insight II (Biosym/Molecular Simulations, Inc., San Diego) or Quanta (Molecular Simulations, Inc., Burlington MA), and distances and spherical volumes may be generated using tools available within those programs.

III.   Pharmaceutical Compositions and Methods of Inhibiting HIV Protease or
         an HIV Infection

The compounds of the invention are useful for inhibiting retroviral protease, in particular HIV protease, in vitro or in vivo (especially in mammals and in particular in humans). The compounds of the present invention are also useful for the inhibition of retroviruses in vivo, especially human immunodeficiency virus (HIV). The compounds of the present invention are also useful for the treatment or prophylaxis of diseases caused by retroviruses, especially acquired immune deficiency syndrome or an HIV infection in a human or other mammal.

Total daily dose administered to a human or other mammal host in single or divided doses may be in amounts, for example, from 0.001 to 300 mg/kg body weight daily and more usually 0.1 to 20 mg/kg body weight daily. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

The compounds of the present invention may be administered orally, parenterally, sublingually, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically

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acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparations, for example, sterile injectable aqueous or oleagenous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-propanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

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The compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically aceptable and metabolizable lipid capabale of forming liposomes can be used. The present compositions in liposome form can contain, in addition to the compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natureal and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

Some preferred dosage forms for the compounds of this invention are disclosed in U.S. Patent Application No. 08/_____, filed November 21, 1996, in the names of J. Lipari, L.A. Al-Razzak, S. Ghosh and R. Gao and which is entitled Pharmaceutical Composition, which is incorporated herein by reference.

A preferred dosage form for the compounds of this invention comprises a solution of (a) a compound of the formula I in the amount of from about 1% to about 50% (preferably, from about 5% to about 30%) by weight of the total solution and (b) polyoxyl 35 castor oil in the amount of from about 0% to about 20% (preferably, from about 5% to about 10%) by weight of the total solution, in a pharmaceutically acceptable organic solvent which comprises (i) oleic acid in the amount of from about   20% to about 99% (preferably, from about 30% to about 70%; more preferably, from about 40% to about 65%) by weight of the total solution or (ii) a mixture of (1) oleic acid in the amount of from about   20% to about 99% (preferably, from about 30% to about 70%; more preferably, from about 40% to about 65%) by weight of the total solution and (2) ethanol or propylene glycol or a mixture thereof in the amount of from about 0% to about 12% (preferably, about 10%) by weight of the total solution. In an even more preferred embodiment of the invention, the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule.

A most preferred composition of the invention comprises a solution of

(a) a compound of the formula I in the amount of about 30% by weight of the total solution and (b) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution, in a pharmaceutically acceptable organic solvent which comprises a mixture of (1) oleic acid in the amount of about 50% by weight of the total solution and (2) ethanol in the amount of about 10% by weight of the total solution. In a most preferred embodiment of the invention, the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule and the solution also comprises an antioxidant (preferably, BHT (butylated hydroxytoluene)) in the amount of from about 0.01% to about 0.08% by weight of the total solution (preferably, from about 0.01% to about 0.05% by weight of the total solution).

An example of such a composition and its preparation is provided below.

Component	% By Weight
compound of Example 2B (free base)	30
Ethanol (USP, 200 proof)	10
polyoxyl 35 castor oil (Cremophor® EL)	10
Oleic acid, 6321, NF	50
Butylated hydroxy toluene (BHT), NF	0.01

Preparation of the above composition:

The mixing tank was purged with nitrogen. Oleic acid (499.9 g) and ethanol (100g) were mixed in the tank. The butylated hydroxytoluene (0.1 g) was charged into the tank and mixed until the solution was clear. The Compound of Example 2B (300 g) was slowly charged into the tank and mixed until the solution was clear. The polyoxyl 35 castor oil (100 g)was added to the tank and mixed. The resulting solution was filled into soft elastic capsules (0.333 g of solution/SEC) to provide a dosage of 100 mg of compound of Example 2B/SEC or 0.667 g/SEC to provide a dosage of 200 mg of compound of Example 2B/SEC.

While the compound of the invention can be administered as the sole active pharmaceutical agent, it can also be used in combination with one or

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more immunomodulators, antiviral agents, other antiinfective agents or vaccines. Other antiviral agents to be administered in combination with a compound of the present invention include AL-721, beta interferon, polymannoacetate, reverse transcriptase inhibitors (for example, dideoxycytidine (ddC; zalcitabine), dideoxyinosine (ddI; didanosine), BCH-189, AzdU, carbovir, ddA, d4C, d4T (stavudine), 3TC (lamivudine) DP-AZT, FLT (fluorothymidine), BCH-189, 5-halo-3'-thia-dideoxycytidine, PMEA, bis-POMPMEA, zidovudine (AZT), nevirapine, delviridine, MSA-300, trovirdine and the like), non-nucleoside reverse transcriptase inhibitors (for example, R82193, L-697,661, BI-RG-587 (nevirapine), retroviral protease inhibitors (for example, HIV protease inhibitors such as ritonavir, Ro 31-8959 (saquinavir), SC-52151, VX-478, AG1343 (nelfinavir), BMS 186,318, SC-55389a, BILA 1096 BS, DMP-323, DMP-450, KNI-227, KNI-272, U-140690, N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide (MK-639; indinavir), 5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)-phenylmethylhexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide, 1-Naphthoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide (i.e., 1-Naphthoxyacetyl-Mta-(2S,3S)-AHPBA-Thz-NH-tBu), 5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide (i.e., iQoa-Mta-Apns-Thz-NHtBu) and the like), HEPT compounds, L,697,639, R82150, U-87201E and the like), HIV integrase inhibitors (Zintevir and the like), TAT inhibitors (for example, RO-24-7429 and the like), trisodium phosphonoformate, HPA-23, eflonithine, Peptide T, Reticulose (nucleophosphoprotein), ansamycin LM 427, trimetrexate, UA001, ribavirin, alpha interferon, oxetanocin, oxetanocin-G, cylobut-G, cyclobut-A, ara-M, BW882C87, foscarnet, BW256U87, BW348U87, L-693,989, BV ara-U, CMV triclonal antibodies, FIAC, HOE-602, HPMPC, MSL-109, TI-23, trifluridine, vidarabine, famciclovir, penciclovir, acyclovir, ganciclovir, castanospermine, rCD4/CD4-IgG, CD4-PE40, butyl-DNJ, hypericin, oxamyristic acid, dextran sulfate and pentosan polysulfate. Immunomodulators that can be administered in combination with the compound of the present invention include bropirimine, Ampligen, anti-human alpha interferon antibody, colony stimulting factor, CL246,738, Imreg-1, Imreg-2, diethydithiocarbamate, interleukin-2, alpha-

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interferon, inosine pranobex, methionine enkephalin, muramyl-tripeptide, TP-5, erythropoietin, naltrexone, tumor necrosis factor, beta interferon, gamma interferon, interleukin-3, interleukin-4, autologous CD8+ infusion, alpha interferon immunoglobulin, IGF-1, anti-Leu-3A, autovaccination, biostimulation, extracorporeal photophoresis, cyclosporin, rapamycin, FK-565, FK-506, G-CSF, GM-CSF, hyperthermia, isopinosine, IVIG, HIVIG, passive immunotherapy and polio vaccine hyperimmunization. Other antiinfective agents that can be administered in combination with the compound of the present invention include pentamidine isethionate. Any of a variety of HIV or AIDS vaccines (for example, gp120 (recombinant), Env 2-3 (gp120), HIVAC-1e (gp120), gp160 (recombinant), VaxSyn HIV-1 (gp160), Immuno-Ag (gp160), HGP-30, HIV-Immunogen, p24 (recombinant), VaxSyn HIV-1 (p24) can be used in combination with the compound of the present invention.

Other agents that can be used in combination with the compound of this invention are ansamycin LM 427, apurinic acid, ABPP, AI-721, carrisyn, AS-101, avarol, azimexon, colchicine, compound Q, CS-85, N-acetyl cysteine, (2-oxothiazolidine-4-carboxylate), D-penicillamine, diphenylhydantoin, EL-10, erythropoieten, fusidic acid, glucan, HPA-23, human growth hormone, hydroxchloroquine, iscador, L-ofloxacin or other quinolone antibiotics, lentinan, lithium carbonate, MM-1, monolaurin, MTP-PE, naltrexone, neurotropin, ozone, PAI, panax ginseng, pentofylline, pentoxifylline, Peptide T, pine cone extract, polymannoacetate, reticulose, retrogen, ribavirin, ribozymes, RS-47, Sdc-28, silicotungstate, THA, thymic humoral factor, thymopentin, thymosin fraction 5, thymosin alpha one, thymostimulin, UA001, uridine, vitamin B12 and wobemugos.

Other agents that can be used in combination with the compound of this invention are antifungals such as amphotericin B, clotrimazole, flucytosine, fluconazole, itraconazole, ketoconazole and nystatin and the like.

Other agents that can be used in combination with the compound of this invention are antibacterials such as amikacin sulfate, azithromycin, ciprofloxacin, tosufloxacin, clarithromycin, clofazimine, ethambutol, isoniazid, pyrazinamide, rifabutin, rifampin, streptomycin and TLC G-65 and the like.

Other agents that can be used in combination with the compound of this invention are anti-neoplastics such as alpha interferon, COMP

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(cyclophosphamide, vincristine, methotrexate and prednisone), etoposide, mBACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone), PRO-MACE/MOPP(prednisone, methotrexate (w/leucovin rescue), doxorubicin, cyclophosphamide, taxol, etoposide/mechlorethamine, vincristine, prednisone and procarbazine), vincristine, vinblastine, angioinhibins, pentosan polysulfate, platelet factor 4 and SP-PG and the like.

Other agents that can be used in combination with the compound of this invention are drugs for treating neurological disease such as peptide T, ritalin, lithium, elavil, phenytoin, carbamazipine, mexitetine, heparin and cytosine arabinoside and the like.

Other agents that can be used in combination with the compound of this invention are anti-protozoals such as albendazole, azithromycin, clarithromycin, clindamycin, corticosteroids, dapsone, DIMP, eflornithine, 566C80, fansidar, furazolidone, L,671,329, letrazuril, metronidazole, paromycin, pefloxacin, pentamidine, piritrexim, primaquine, pyrimethamine, somatostatin, spiramycin, sulfadiazine, trimethoprim, TMP/SMX, trimetrexate and WR 6026 and the like.

Among the preferred agents for inhibition or treatment of HIV or AIDS in combination with the compound of this invention are reverse transcriptase inhibitors, especially, AZT (zidovudine), ddI (didanosine), ddC (zalcitabine), d4T (stavudine), 3TC (lamivudine), nevirapine, delviridine, trovirdine, PMEA, bis-POMPMEA and MSA-300.

Other preferred agents for inhibition or treatment of HIV or AIDS in combination with the compound of this invention are HIV protease inhibitors, especially, ABT-538 (ritonavir) and related compounds, disclosed in U.S. Patent No. 5,541,206, issued July 30, 1996 and U.S. Patent No. 5,491,253, issued February 13, 1996 which are both incorporated by reference herein, N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide (i.e., indinavir) and related compounds, disclosed in European Patent Application No. EP541168, published May 12, 1993, and U.S. Patent No. 5,413,999, issued May 9, 1995 which are both incorporated herein by reference;

N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-
L-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide (i.e.,
saquinavir) and related compounds, disclosed in U.S. Patent No. 5,196,438,
issued March 23, 1993, which is incorporated herein by reference;
5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)-phenylmethylhexanoyl-(L)-Val-
(L)-Phe-morpholin-4-ylamide and related compounds, disclosed in European
Patent Application No. EP532466, published March 17, 1993, which is
. incorporated herein by reference;
1-Naphthoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-
butanoyl-1,3-thiazolidine-4-t-butylamide (i.e., 1-Naphthoxyacetyl-Mta-(2S,3S)-
AHPBA-Thz-NH-tBu), 5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-
amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide (i.e., iQoa-Mta-
Apns-Thz-NHtBu) and related compounds, disclosed in European Patent
Application No. EP490667, published June 17, 1992 and Chem. Pharm. Bull.
40 (8) 2251 (1992), which are both incorporated herein by reference;
[1S-[1R*(R*),2S*]}-N^1[3-[[[(1,1-dimethylethyl)amino]carbonyl](2-
methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-
quinolinylcarbonyl)amino]-butanediamide (i.e., SC-52151) and related
compounds, disclosed in PCT Patent Application No. WO92/08701, published
May 29, 1992 and PCT Patent Application No. WO93/23368, published
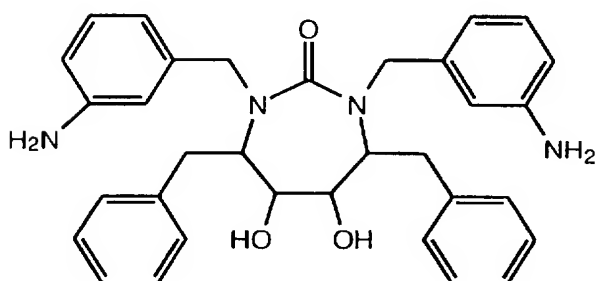November 25, 1993, both of which are incorporated herein by reference;
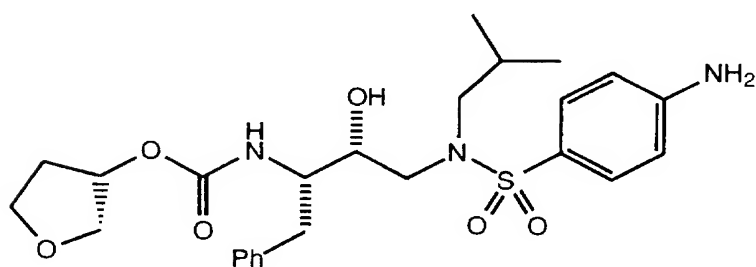
(i.e., VX-478) and related compounds, disclosed in PCT Patent Application No.
WO94/05639, published March 17, 1994, which is incorporated herein by
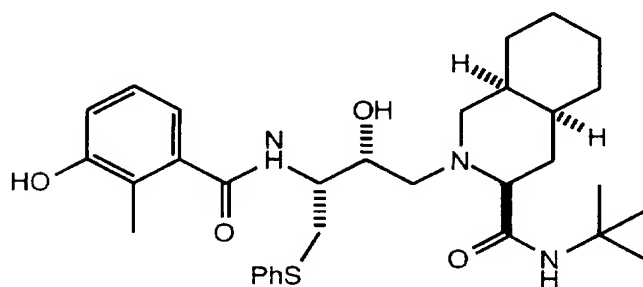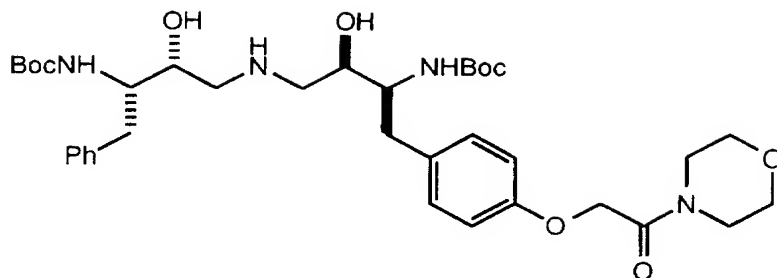reference;

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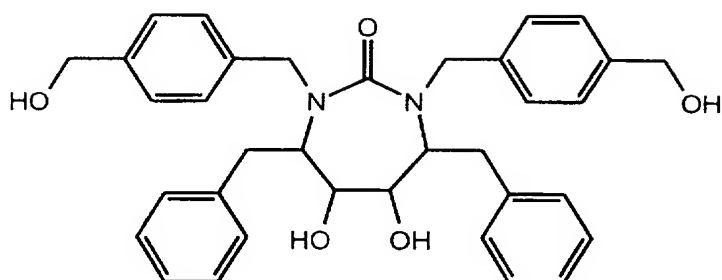
(i.e., DMP-323) or

(i.e., DMP-450)

and related compounds, disclosed in PCT Patent Application No. WO93/07128, published April 15, 1993, which is incorporated herein by reference;
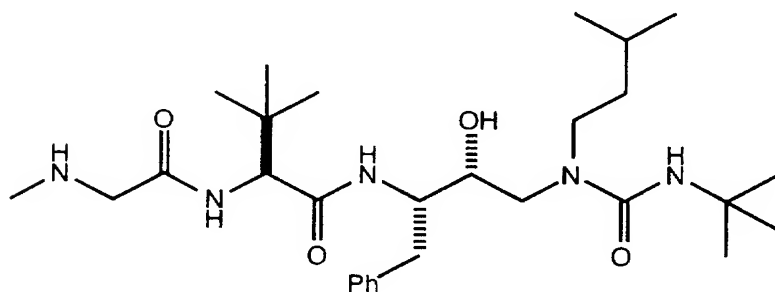

(i.e., AG1343, (nelfinavir)), disclosed in PCT Patent Application No. WO95/09843, published April 13, 1995 and U.S. Patent No. 5,484,926, issued January 16, 1996, which are both incorporated herein by reference;
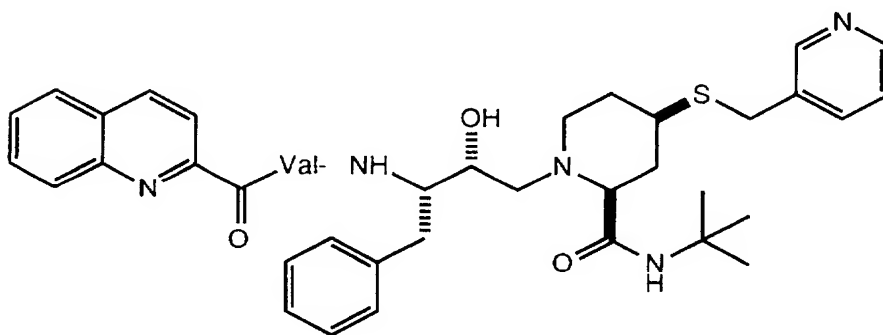
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(i.e., BMS 186,318)

disclosed in European Patent Application No. EP580402, published January 26, 1994, which is incorporated herein by reference;
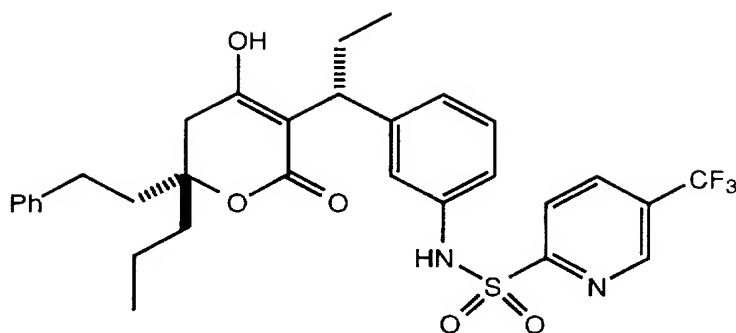

(i.e., SC-55389a)

disclosed at 2nd National Conference on Human Retroviruses and Related Infections, (Washington, D.C., Jan. 29 - Feb. 2, 1995), Session 88; and

(i.e., BILA 1096 BS) and related compounds disclosed in European Patent Application No. EP560268, published September 15, 1993, which is incorporated herein by reference; and

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(i.e., U-140690) and related compounds disclosed in PCT Patent Application No. WO 9530670, published November 16, 1995, which is incorporated herein by reference; or a pharmaceutically acceptable salt of any of the above.

In a most preferred combination, a compound of this invention is administered in combination with ritonavir. Such a combination is especially useful for inhibiting HIV protease in a human. Such a combination is also especially useful for inhibiting or treating an HIV infection in a human. When used in such a combination the compound of this invention and ritonavir can be administered as separate agents at the same or different times or they can be formulated as a single composition comprising both compounds.

When administered in combination with a compound of this invention, ritonavir causes an improvement in the pharmacokinetics (i.e., increases half-life, increases the time to peak plasma concentration, increases blood levels) of the compound of this invention.

Preferred dosage forms for ritonavir include (a) a liquid dosage form for oral administration as disclosed in U.S. Patent No. 5,484,801, issued January 19, 1996, which is incorporated herein by reference, (b) an encapsulated solid or semi-solid dosage form as disclosed in PCT Patent Application No. WO95/07696, published March 23, 1995 and U.S. Serial No. 08/402,690, filed March 13, 1995, both of which are incorporated herein by reference and (c) an encapsulated solid dosage form as disclosed in PCT Patent Application No. WO95/09614, published April 13, 1995 and U.S. Patent No. 5,559,158, issued September 24, 1996, both of which are incorporated herein by reference.

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Other examples of preferred dosage forms for ritonavir are disclosed in U.S. Patent Application No. 08/_____, filed November 21, 1996, in the names of J. Lipari, L.A. Al-Razzak, S. Ghosh and R. Gao and which is entitled Pharmaceutical Composition, which is incorporated herein by reference.

A preferred composition for ritonavir comprises a solution of (a) ritonavir in the amount of from about 1% to about 30% (preferably, from about 5% to about 25%) by weight of the total solution and (b) polyoxyl 35 castor oil in the amount of from about 0% to about 20% (preferably, from about 5% to about 10%) by weight of the total solution, in a pharmaceutically acceptable organic solvent which comprises (i) oleic acid in the amount of from about 15% to about 99% (preferably, from about 30% to about 70%; more preferably, from about 40% to about 65%) by weight of the total solution or (ii) a mixture of (1) oleic acid in the amount of from about 15% to about 99% (preferably, from about 30% to about 70%; more preferably, from about 40% to about 65%) by weight of the total solution and (2) ethanol or propylene glycol or a mixture thereof in the amount of from about 0% to about 12% (preferably, about 10%) by weight of the total solution. In an even more preferred embodiment of the invention, the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule and the solution also comprises an antioxidant (preferably, BHT (butylated hydroxytoluene)) in the amount of from about 0.01% to about 0.08% by weight of the total solution (preferably, from about 0.01% to about 0.05% by weight of the total solution).

Examples of such a composition and its preparation are provided below.

Component	% By Weight
ritonavir (free base)	20
Ethanol (USP, 200 proof)	10
polyoxyl 35 castor oil (Cremophor® EL)	5
Oleic acid, 6321, NF	65
Butylated hydroxy toluene (BHT), NF	0.01

Preparation of the above composition:

The mixing tank was purged with nitrogen. Oleic acid (649.9 g) and ethanol (100g) were mixed in the tank. This solution was warmed to about

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33°C (29-37°C) and maintained at that temperature. The butylated hydroxytoluene (0.1 g) was charged into the tank and mixed until the solution was clear. The ritonavir (200 g) was slowly charged into the tank and mixed until the solution was clear. The polyoxyl 35 castor oil (50 g) was added to the tank and mixed. Heating was discontinued and the solution allowed to cool to amibient temperature (20-30°C). The resulting solution was filled into soft elastic capsules (0.5 g of solution/SEC) to provide a dosage of 100 mg of ritonavir/SEC or 1.0 g/SEC to provide a dosage of 200 mg of ritonavir/SEC.

Component	% By Weight
ritonavir (free base)	20
Ethanol (USP, 200 proof)	10
polyoxyl 35 castor oil (Cremophor® EL)	10
Oleic acid, 6321, NF	60
Butylated hydroxy toluene (BHT), NF	0.01

Preparation of the above composition:

The mixing tank was purged with nitrogen. Oleic acid (599.9 g) and ethanol (100g) were mixed in the tank. This solution was warmed to about 33°C (29-37°C) and maintained at that temperature. The butylated hydroxytoluene (0.1 g) was charged into the tank and mixed until the solution was clear. The ritonavir (200 g) was slowly charged into the tank and mixed until the solution was clear. The polyoxyl 35 castor oil (100 g)was added to the tank and mixed. Heating was discontinued and the solution allowed to cool to amibient temperature (20-30°C). The resulting solution was filled into soft elastic capsules (0.5 g of solution/SEC) to provide a dosage of 100 mg of ritonavir/SEC or 1.0 g/SEC to provide a dosage of 200 mg of ritonavir/SEC.

Examples of preferred single dosage forms comprising both ritonavir and a compound of the formula I are also disclosed in U.S. Patent Application No. 08/_____, filed November 21, 1996, in the names of J. Lipari, L.A. Al-Razzak, S. Ghosh and R. Gao and which is entitled Pharmaceutical Composition, which is incorporated herein by reference.

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A preferred composition for a single dosage form comprising both ritonavir and a compound of the formula I comprises a solution of (a) a mixture of ritonavir in the amount of from about 1% to about 30% (preferably, from about 5% to about 25%) by weight of the total solution and a compound of the formula I in the amount of from about 1% to about 50% (preferably, from about 5% to about 40%) by weight of the total solution and (b) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution, in a pharmaceutically acceptable organic solvent which comprises a mixture of (1) oleic acid in the amount of from about 10% to about 88% (preferably, from about 40% to about 65%) by weight of the total solution and (2) ethanol in the amount of about 10% by weight of the total solution. In a most preferred embodiment of the invention, the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule and the solution also comprises an antioxidant (preferably, BHT (butylated hydroxytoluene)) in the amount of from about 0.01% to about 0.08% by weight of the total solution (preferably, from about 0.01% to about 0.05% by weight of the total solution).

Examples of such a composition and its preparation are provided below.

Component	% By Weight
ritonavir (free base)	5
compound of Example 2B (free base)	30
Ethanol (USP, 200 proof)	10
polyoxyl 35 castor oil (Cremophor® EL)	10
Oleic acid, 6321, NF	45
Butylated hydroxy toluene (BHT), NF	0.01

Component	% By Weight
ritonavir (free base)	15
compound Example 2B (free base)	15
Ethanol (USP, 200 proof)	10
polyoxyl 35 castor oil (Cremophor® EL)	10
Oleic acid, 6321, NF	50
Butylated hydroxy toluene (BHT), NF	0.01

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Component	% By Weight
ritonavir (free base)	15
compound Example 2B (free base)	15
Ethanol (USP, 200 proof)	10
polyoxyl 35 castor oil (Cremophor® EL)	5
Oleic acid, 6321, NF	55
Butylated hydroxy toluene (BHT), NF	0.01

Preparation of the above composition:

The mixing tank was purged with nitrogen. Oleic acid (549.9 g) and ethanol (100g) were mixed in the tank.   The butylated hydroxytoluene (0.1 g) was charged into the tank and mixed until the solution was clear. The ritonavir (150 g) was slowly charged into the tank and mixed until the solution was clear. Compound Example 2B (150 g) was slowly charged into the tank and mixed until the solution was clear. The polyoxyl 35 castor oil (100 g) was added to the tank and mixed. The resulting solution was filled into soft elastic capsules (1.0 g of solution/SEC) to provide a dosage of 150 mg each of ritonavir and compound Example 2B/SEC.

Component	% By Weight
ritonavir (free base)	15
compound Example 2B (free base)	5
Ethanol (USP, 200 proof)	10
polyoxyl 35 castor oil (Cremophor® EL)	10
Oleic acid, 6321, NF	60
Butylated hydroxy toluene (BHT), NF	0.01

Total daily dose of ritonavir (administered in combination with a compound of this invention) to be administered to a human or other mammal host in single or divided doses may be in amounts, for example, from 0.001 to 300 mg/kg body weight daily and more usually 0.1 to 10 mg of ritonavir.

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Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

In the compositions which comprise a mixture of ritonavir and the compound of Example 2B, the ratio (w/w) of ritonavir to the compound of Example 2B ranges from about 1:16 to about 5:1 (preferably, from about 1:6 to about 3:1).

In another most preferred combination, a compound of this invention is administered in combination with ritonavir and one or more reverse transcriptase inhibitors (preferably, one or more compounds selected from the group consisting of AZT (zidovudine), ddI (didanosine), ddC (zalcitabine), d4T (stavudine) and 3TC (lamivudine)). Such a combination is especially useful for inhibiting or treating an HIV infection in a human. When used in such a combination the compound of this invention and ritonavir and one or more reverse transcriptase inhibitors can be administered as separate agents at the same or different times or they can be formulated as compositions comprising two or more of the compounds. A particularly preferred therapeutic combination comprises a compound of the formula I (especially, the compound of Example 2B) in combination with ritonavir, AZT and 3TC.

It will be understood that agents which can be combined with the compound of the present invention for the inhibition, treatment or prophylaxis of AIDS or an HIV infection are not limited to those listed above, but include in principle any agents useful for the treatment or prophylaxis of AIDS or an HIV infection.

When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

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CLAIMS

WHAT IS CLAIMED IS:

1.   A compound, which when bound to HIV protease, contains at least one ring atom of a heterocycle in either the protease S2 or S2' subsite, wherein the heterocycle (a) comprises 4 to 7 ring atoms, (b) contains at least one ring N atom, and (c) contains at least one ring C atom which is substituted with oxo (=O), thioxo (=S) or imino (=NH).

2.   The compound of claim 1, which when bound to the protease, binds to the active site of the protease.

3.   The compound of claim 1, which when bound to the protease, further comprises a non-hydrogen atom in either the S1 or S1' subsite of the protease.

4.   The compound of claim 3, which when bound to the protease, lacks a non-hydrogen atom in both the S3 and S3' subsites of the protease, which S3 and S3' subsites do not include any of the S1 and S1' subsites, respectively.

5.   The compound of claim 1 wherein the heterocycle is a 5- or 6-membered ring.

6.   The compound of claim 5 wherein the heterocycle has two non-adjacent ring N atoms and at least one ring C atom which is substituted with oxo (=O).

7.   The compound of claim 6 wherein at least one of the ring N atoms is of the structure NH.

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8.   The compound of claim 5 wherein the heterocycle ring has from 0 to 2 double bonds.

9.   The compound of claim 7 wherein the ring N atom of the NH structure is located within a range of from about 2.4 Å to about 3.7 Å of the backbone nitrogen atom of either residue 30 or residue 130 of the protease when the compound is bound to the protease.

10.   The compound of claim 7 wherein the O of the C=O structure is located within a range of from about 2.4 Å to about 3.7 Å of the backbone nitrogen atom of either residue 30 or residue 130 of the protease when the compound is bound to the protease.

11.   The compound of claim 7 wherein both the N atom of the NH group and the O of the C=O group are located within a range of from about 2.4 Å to about 3.7 Å of the backbone nitrogen atom of either residue 30 or residue 130 of the protease when the compound is bound to the protease.

12.   The compound of claim 1, which when bound to the protease, comprises a non-hydrogen atom in a first spherical volume having a radius of about 3.0 Å and a center point defined by at least three loci selected from the group of first loci consisting of 5.0 Å to 6.0 Å from the alpha carbon of residue 27 of the protease, 5.0 Å to 6.0 Å from the alpha carbon of residue 127 of the protease, 6.3 Å to 7.5 Å from the alpha carbon of residue 50 of the protease, and 6.3 Å to 7.5 Å from the alpha carbon of residue 150 of the protease.

13.   The compound of claim 1, which when bound to the protease, comprises at least one of the heterocycle ring atoms in either a second or a third spherical volume wherein the second spherical volume has a radius in the range of from about 2.5 Å to about 4.0 Å and a center point defined by at least three loci selected from the group of second loci consisting of 3.7 Å to 4.5 Å from the alpha carbon of residue 28 of the protease, 4.2 Å to 5.4 Å from the alpha carbon of residue 30 of the protease, 7.6 Å to 8.3 Å from the alpha carbon

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of residue 32 of the protease, and 6.5 Å to 7.0 Å from the alpha carbon of residue 48 of the protease and wherein the third spherical volume has a radius in the range of from 2.5 Å to about 4.0 Å and a center point defined by at least three loci selected from the group of third loci consisting of 3.7 Å to 4.5 Å from the alpha carbon of residue 28 of the protease, 4.2 Å to 5.4 Å from the alpha carbon of residue 30 of the protease, 7.6 Å to 8.3 Å from the alpha carbon of residue 32 of the protease, and 6.5 Å to 7.0 Å from the alpha carbon of residue 48 of the protease.

14.   The compound of claim 13 wherein the center points of the second and third spherical volumes are defined by four loci selected from the groups of the second and third loci, respectively.

15.   The compound of claim 13 wherein the radii of the second and third spherical volumes are each independently in the range of from about 3.0 Å to about 4.0 Å.

16.   The compound of claim 13 wherein the radii of the second and third spherical volumes are each independently in the range of from about 3.5 Å to about 4.0 Å.

17.   The compound of claim 1, which when bound to the protease comprises a non-hydrogen atom in either a fourth or fifth spherical volume wherein the fourth spherical volume has a radius in the range of from about 2.5 Å to about 4.0 Å and a center point defined by at least three loci selected from the group of fourth loci consisting of 3.2 Å to 3.7 Å from the alpha carbon of residue 49 of the protease, 4.1 Å to 4.5 Å from the alpha carbon of residue 50 of the protease, 12.4 Å to 12.8 Å from the alpha carbon of residue 108 of the protease, 13.0 Å to 13.4 Å from the alpha carbon of residue 110 of the protease, 11.0 Å to 11.4 Å from the alpha carbon of residue 125 of the protease, 5.7 Å to 6.1 Å from the alpha carbon of residue 182 of the protease, and 8.4 Å to 8.8 Å from the alpha carbon of residue 184 of the protease and wherein the fifth spherical volume has a radius in the range of from about 2.5 Å to about 4.0 Å and a center point defined by at least three loci selected from the group of five

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loci consisting of 3.2 Å to 3.7 Å from the alpha carbon of residue 149 of the protease, 4.1 Å to 4.5 Å from the alpha carbon of residue 150 of the protease, 12.4 Å to 12.8 Å from the alpha carbon of residue 8 of the protease, 13.0 Å to 13.4 Å from the alpha carbon of residue 10 of the protease, 11.0 Å to 11.4 Å from the alpha carbon of residue 25 of the protease, 5.7 Å to 6.1 Å from the alpha carbon of residue 82 of the protease, and 8.4 Å to 8.8 Å from the alpha carbon of residue 84 of the protease.

18.   The compound of claim 17 wherein the radii of the fourth and fifth spherical volumes are each independently in the range of from about 3.0 Å to about 4.0 Å.

19.   The compound of claim 17 wherein the radii of the fourth and fifth spherical volumes are each independently in the range of from about 3.5 Å to about 4.0 Å.

20.   The compound of claim 17 wherein the center points of the fourth and fifth spherical volumes are each independently defined by at least four loci selected from the groups of the fourth and fifth loci, respectively.

21.   The compound of claim 17 wherein the center points of the fourth and fifth spherical volumes are each independently defined by at least five loci selected from the groups of the fourth and fifth loci, respectively.

22.   The compound of claim 17 wherein the center points of the fourth and fifth spherical volumes are each independently defined by at least six loci selected from the groups of the fourth and fifth loci, respectively.

23.   The compound of claim 17, which when bound to the protease, lacks a non-hydrogen atom in both a sixth and a seventh spherical volume, wherein the sixth spherical volume has a radius in the range of from about 2.5 Å to about 4.0 Å, a center point defined by at least three loci selected from the group of sixth loci consisting of 7.7 Å to 8.2 Å from the alpha carbon of residue 49 of the protease, 9.8 Å to 10.2 Å from the alpha carbon of residue 50 of the

protease, 9.6 Å to 10.0 Å from the alpha carbon of residue 108 of the protease,
10.4 Å to 10.8 Å from the alpha carbon of residue 110 of the protease, 12.7 Å to
13.1 Å from the alpha carbon of residue 125 of the protease, 5.4 Å to 5.8 Å from
the alpha carbon of residue 182 of the protease, and 10.1 Å to 10.6 Å from the
alpha carbon of residue 184 of the protease, and which sixth spherical volume
does not include any of the fourth spherical volume; and wherein the seventh
spherical volume has a radius in the range of from about 2.5 Å to about 4.0 Å, a
center point defined by at least three loci selected from the group of seventh
loci consisting of 7.7 Å to 8.2 Å from the alpha carbon of residue 149 of the
protease, 9.8 Å to 10.2 Å from the alpha carbon of residue 150 of the protease,
9.6 Å to 10.0 Å from the alpha carbon of residue 8 of the protease, 10.4 Å to
10.8 Å from the alpha carbon of residue 10 of the protease, 12.7 Å to 13.1 Å
from the alpha carbon of residue 25 of the protease, 5.4 Å to 5.8 Å from the
alpha carbon of residue 82 of the protease, and 10.1 Å to 10.6 Å from the alpha
carbon of residue 84 of the protease, wherein the seventh spherical volume
does not include any of the fifth spherical volume.

24.   The compound of claim 23 wherein the radii of the sixth and
seventh spherical volumes are each independently in the range of from about
3.0 Å to about 4.0 Å.

25   The compound of claim 23 wherein the radii of the sixth and
seventh spherical volumes are each independently in the range of from about
3.5 Å to about 4.0 Å.

26.   The compound of claim 23 wherein the center points of the sixth
and seventh spherical volume are each independently defined by at least four
loci selected from the groups of the sixth and seventh loci, respectively.

27.   The compound of claim 23 wherein the center points of the sixth
and seventh spherical volume are each independently defined by at least five
loci selected from the groups of the sixth and seventh loci, respectively.

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28. The compound of claim 23 wherein the center points of the sixth and seventh spherical volume are each independently defined by at least six loci selected from the groups of the sixth and seventh loci, respectively.

29. A pharmaceutical composition for inhibiting HIV protease comprising a pharmaceutical carrier and a therapeutically effective amount of the compound of claim 1.

30. A process for inhibiting HIV protease comprising administering to a human in need of such treatment a therapeutically effective amount of the compound of claim 1.

31. A process for inhibiting an HIV infection comprising administering to a human in need of such treatment a therapeutically effective amount of the compound of claim 1.

32. A process for inhibiting an HIV infection comprising administering to a human in need of such treatment a therapeutically effective amount of the compound of claim 1 in combination with a therapeutically effective amount of a reverse transcriptase inhibitor or a combination of reverse transcriptase inhibitors.

33. The process of claim 32 wherein the reverse transcriptase inhibitor is AZT (zidovudine), ddI (didanosine), ddC (zalcitabine), d4T (stavudine), 3TC (lamivudine), nevirapine, delviridine, trovirdine, PMEA, bis-POMPMEA or MSA-300.

34. A process for inhibiting an HIV infection comprising administering to a human in need of such treatment a therapeutically effective amount of the compound of claim 1 in combination with a therapeutically effective amount of another HIV protease inhibitor or a combination of HIV protease inhibitors.

35. The process of claim 34 wherein the other HIV protease inhibitor is ritonavir, saquinavir, , indinavir,
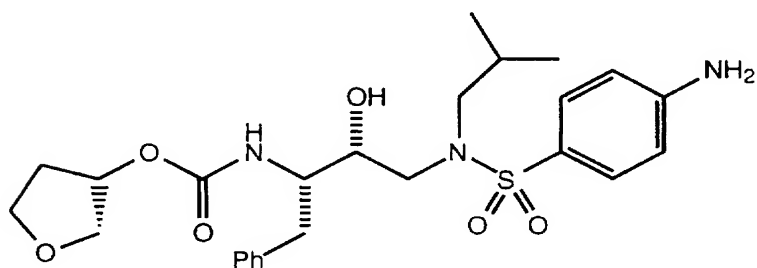
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5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)-phenylmethylhexanoyl-(L)-Val-(L)-
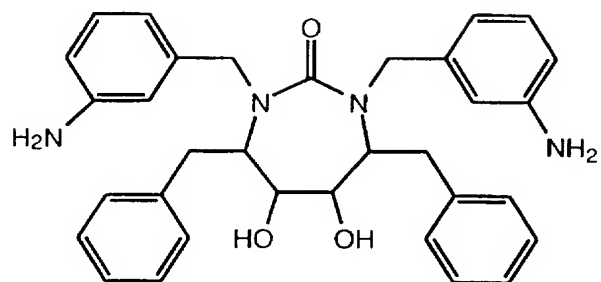Phe-morpholin-4-ylamide;

1-Naphthoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl-
1,3-thiazolidine-4-t-butylamide;

5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-
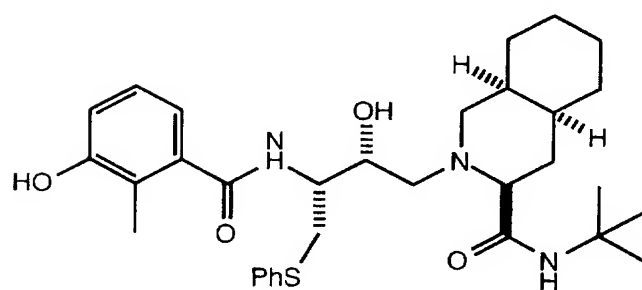butanoyl-1,3-thiazolidine-4-t-butylamide;

(1S-(1R*(R*),2S*)}-N^1(3-((((1,1-dimethylethyl)amino)carbonyl)(2-
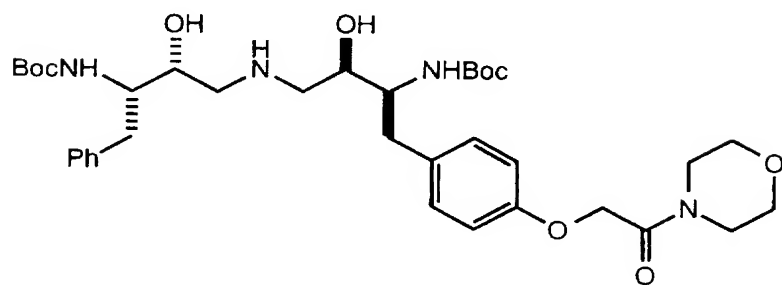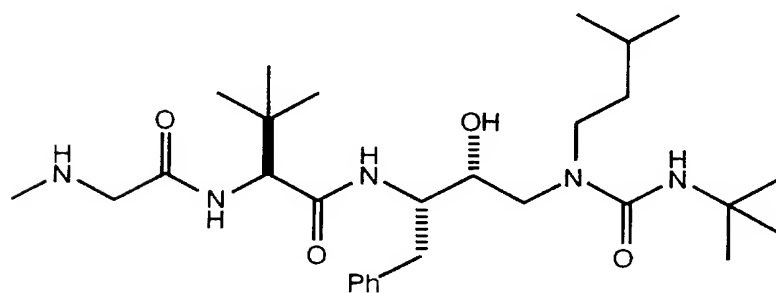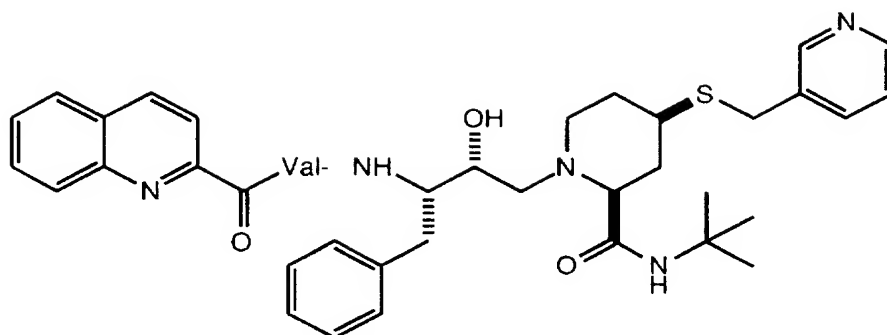methylpropyl)amino)-2-hydroxy-1-(phenylmethyl)propyl)-2-((2-
quinolinylcarbonyl)amino)-butanediamide;
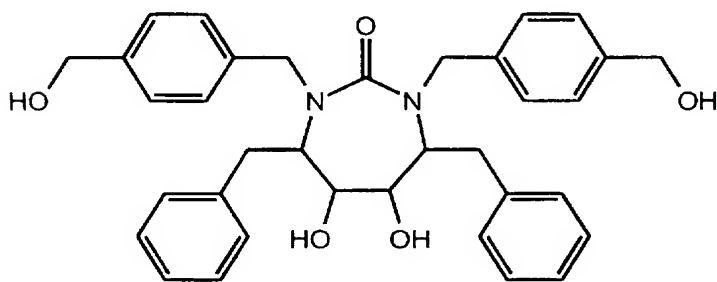
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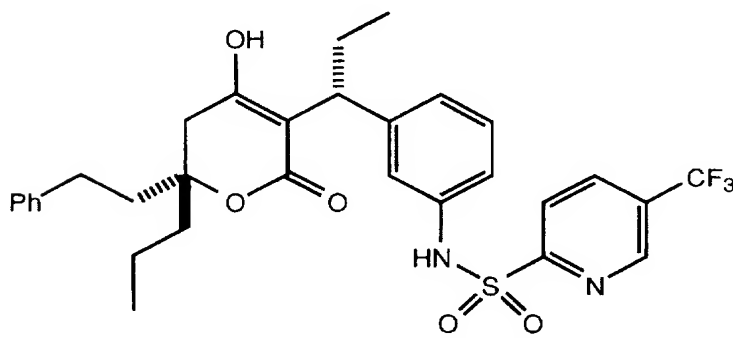
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or a pharmaceutically acceptable salt thereof, or a combination of two or more of these HIV protease inhibitors.

36.   A process for inhibiting HIV protease in a human having resistance to the inhibitory activity of a protease inhibitor, the process comprising administering to the human a therapeutically effective amount of the compound of claim 1.

37.   The process of claim 36 wherein the HIV protease is ritonavir, saquinavir, , indinavir,

5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)-phenylmethylhexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide;
1-Naphthoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide;
5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide;
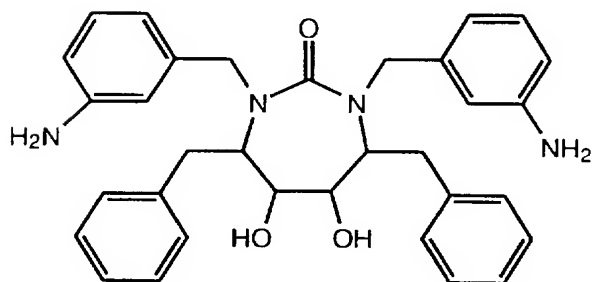
-157-

(1S-(1R*(R*),2S*)}-N¹(3-(((((1,1-dimethylethyl)amino)carbonyl)(2-methylpropyl)amino)-2-hydroxy-1-(phenylmethyl)propyl)-2-((2-quinolinylcarbonyl)amino)-butanediamide;
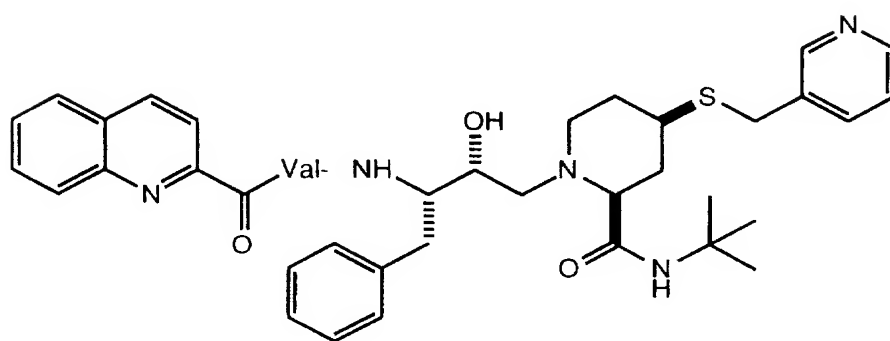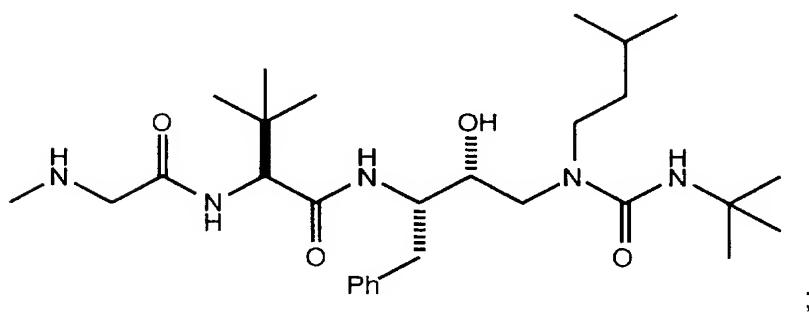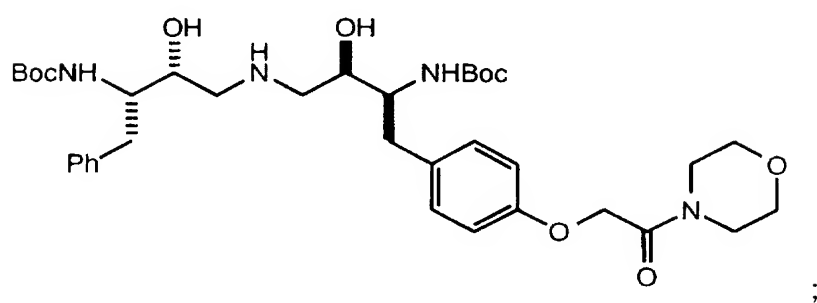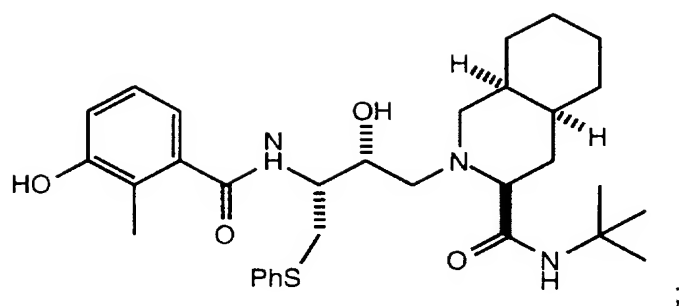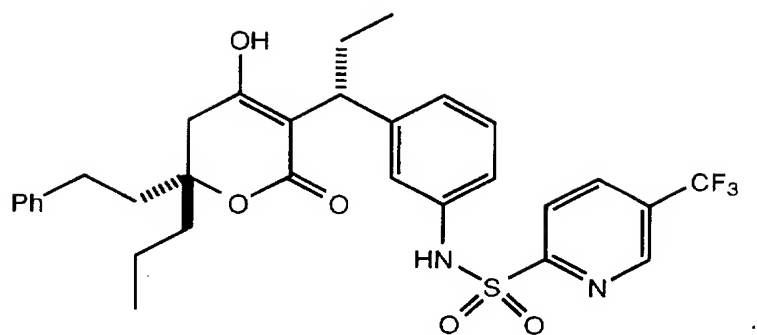

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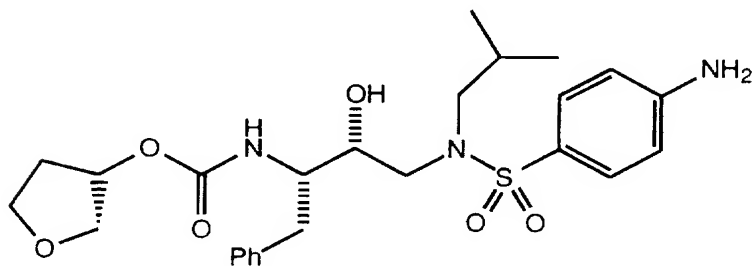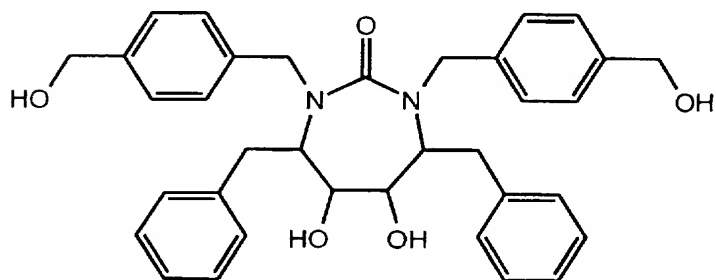
-158-

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; and

-159-

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or a pharmaceutically acceptable salt thereof, or a combination of two or more of these HIV protease inhibitors.

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D233/32 C07D239/10 C07D239/22 C07D207/40 C07D207/26
C07D241/08 C07D263/22 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category°	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 342 541 A (ABBOTT) 23 November 1989 see page 1 - page 20; claims ---	1,2
A	EP 0 580 402 A (SQUIBB & SONS) 26 January 1994 see page 127 - page 236; claims; examples 102-250 -----	1,2

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

19 March 1997

Date of mailing of the international search report

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Authorized officer

Francois, J

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INTERNATIONAL SEARCH REPORT

Box I   Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐   Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒   Claims Nos.:   1-36
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

As the wording of claim 1 is not clear enough that it doesn't comply with Art.6 PCT, the search has been based on the examples prepared in the description and on their intermediates. Their activity were also taken into consideration.

3. ☐   Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II   Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐   As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐   As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐   As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐   No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest   ☐   The additional search fees were accompanied by the applicant's protest.

☐   No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 342541 A	23-11-89	AU 3566089 A		29-11-89
		EP 0415981 A		13-03-91
		JP 3504247 T		19-09-91
		WO 8910752 A		16-11-89
EP 580402 A	26-01-94	US 5559256 A		24-09-96
		AU 4165993 A		27-01-94
		CA 2100894 A		21-01-94
		CN 1085546 A		20-04-94
		HU 67090 A		30-01-95
		HU 9500679 A		28-11-95
		JP 6206857 A		26-07-94
		NO 932620 A		21-01-94
		BG 97961 A		31-03-95
		CZ 9301437 A		15-02-95
		PL 299738 A		05-04-94
		SK 76093 A		05-10-94
		ZA 9305243 A		17-02-94